591. *Preparation of Cyanamide.*

By Alexander Lawson and J. O. Stevens.

As crystalline cyanamide is not available commercially in this country, it is usually prepared from calcium cyanamide by the method described in *Inorganic Syntheses* [1] or in *Organic Syntheses*.[2] Both procedures are time-consuming and tedious. For small laboratory preparations the following method, giving no less yield, is quick and more convenient.

Calcium cyanamide (16 g.) is ground with powdered oxalic acid dihydrate (24 g.) and stirred with ether (200 ml.) and water (10 ml.) for 30 min. Some heat is generated but not enough to cause the ether to boil. The suspension is filtered and the solid washed with ether (50 ml.). The ether solution is then shaken with " Biodeminrolit " de-ionising resin (10 g.) for a few minutes and set aside for 1 hr. This removes the small quantity of oxalic acid present. After filtration the ether solution is kept over anhydrous sodium sulphate for 30 min., then evaporated. The crystalline residue of cyanamide may be recrystallised from benzene–ether (yield 2·5—3·0 g.; m. p. 42—44°).

The method is equally applicable to sodium acid cyanamide which gives near quantitative yield.

Royal Free Hospital School of Medicine,
8 Hunter St., London, W.C.1.

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[1] *Inorg. Synth.*, 1950, **3**, 39.
[2] *Org. Synth.*, 1954, **34**, 67.

592. o-*Hydroxybenzenesulphonamide.*

By C. A. Bartram, P. Oxley, D. A. Peak, and J. S. Nicholson.

Raffa [1] described *o*-hydroxybenzenesulphonamide, prepared *via* the diazonium salt of *o*-aminobenzenesulphonamide, as a strongly acidic substance of high melting point (decomposition above 330°) and low solubility in organic solvents. These properties appeared to us to be incompatible with the expected properties of *o*-hydroxybenzenesulphonamide. Chelation, which Raffa [2] invokes in order to explain the high acidity, would be expected to confer a melting point appreciably lower than those of the *m*- and *p*-isomers (165° and 174° respectively). Re-examination of Raffa's product has in fact shown that it is not *o*-hydroxybenzenesulphonamide but the isomeric *o*-aminobenzenesulphonic acid. This follows from the demonstration that the product contains a diazotisable amino-group and is confirmed by the synthesis of *o*-hydroxybenzenesulphonamide of the expected properties by an unambiguous route. To this end, several routes were tried. Demethylation of *o*-methoxybenzenesulphonamide gave unrecognisable products. Reaction of *o*-acetoxybenzenesulphonyl chloride with aqueous ammonia gave a compound, probably *o*-(*o*-hydroxybenzenesulphonyloxy)benzenesulphonamide, as sole product. Reductive elimination of the amino-group of 4-amino-2-hydroxybenzenesulphonamide [3] by diazotisation and hypophosphite reduction also failed. *o*-Hydroxybenzenesulphonamide was finally obtained from *o*-benzyloxyaniline by conversion *via* the diazonium salt into *o*-benzyloxybenzenesulphonyl chloride and thence into the sulphonamide, followed by catalytic debenzylation.

The recognition of Raffa's product as *o*-aminobenzenesulphonic acid provides a simple explanation of the high acidity of the various acyl derivatives,[2] these now being formulated

[1] Raffa, *Il Farm.* (*Ed. Sci.*), 1955, **10**, 532.
[2] *Idem, ibid.*, 1956, **11**, 46.
[3] Thorpe and Williams, *Biochem. J.*, 1941, **35**, 63.

XUM

as *o*-acylaminobenzenesulphonic acids. The formation [4] of tribromoaniline with bromine water becomes the normal reaction,[5] not requiring any Hofmann-like transposition as postulated by Raffa.

Experimental.—o-*Aminobenzenesulphonic acid.* Repetition of Raffa's preparation [1] afforded the product as plates, m. p. >320° (Found: N, 8·4. Calc. for $C_6H_7O_3NS$: N, 8·1%). It gave a highly acidic solution in water (p*H ca.* 1), and the solution after diazotisation gave a strongly positive coupling reaction with alkaline β-naphthol.

o-*Benzyloxybenzenesulphonamide.* The diazonium solution from *o*-benzyloxyaniline [6] (25·0 g.), concentrated hydrochloric acid (28 c.c.), acetic acid (28 c.c.), and sodium nitrite (9·55 g.) in water (30 c.c.) was added to a saturated solution of sulphur dioxide in acetic acid (90 c.c.) and benzene (90 c.c.) containing finely powdered cupric chloride dihydrate (6·0 g.). The mixture was stirred at 40° for 3 hr., cooled, and diluted with water, and crude *o*-benzyloxybenzenesulphonyl chloride isolated in benzene. After removal of benzene the residue was stirred with ammonia (60 c.c.; *d* 0·88) and water (60 c.c.) for 2 hr. and then at 100° for 30 min. o-*Benzyloxybenzenesulphonamide* was extracted from the crude product with 2N-sodium hydroxide (250 c.c.), filtered (charcoal), and acidified with dilute hydrochloric acid, and the precipitate (8·3 g.) recrystallised from aqueous methanol to give colourless needles, m. p. 129—131° (Found: C, 59·3; H, 4·9; N, 5·6. $C_{13}H_{13}O_3NS$ requires C, 59·3; H, 4·9; N, 5·3%).

Acetic anhydride in pyridine at room temperature gave N-*acetyl*-o-*benzyloxybenzenesulphonamide*, prisms (from methanol), m. p. 142—144° (Found: C, 59·1; H, 5·0; N, 4·5. $C_{15}H_{15}O_4NS$ requires C, 59·0; H, 4·9; N, 4·6%).

o-*Hydroxybenzenesulphonamide.* *o*-Benzyloxybenzenesulphonamide (3·15 g.) in acetic acid (150 c.c.) was shaken with hydrogen and 10% palladium–charcoal (1·5 g.) at room temperature. Absorption of hydrogen was complete in 3 min. The filtrate from the catalyst was evaporated to dryness *in vacuo* below 50° and the residue recrystallised from benzene (charcoal) to give o-*hydroxybenzenesulphonamide* (1·5 g.) as needles or plates, m. p. 139—141° [Found: C, 41·8; H, 4·1; N, 8·3; S, 17·9%; *M* (Rast), 172. $C_6H_7O_3NS$ requires C, 41·6; H, 4·05; N, 8·1; S, 18·5%; *M*, 173].

Acetic anhydride in pyridine at room temperature afforded o-*acetoxy*-N-*acetylbenzenesulphonamide*, plates (from benzene), m. p. 115—117·5° (Found: C, 47·3; H, 4·3; N, 5·6. $C_{10}H_{11}O_5NS$ requires C, 46·7; H, 4·3; N, 5·45%). Toluene-*p*-sulphonyl chloride in pyridine at 100° (15 min.) gave a *toluene*-p-*sulphonyl derivative*, colourless prisms (from methanol), m. p. 137—139° (Found: C, 47·3; H, 3·9; N, 4·5. $C_{13}H_{13}O_5NS$ requires C, 47·7; H, 4·0; N, 4·3%), probably the *O*-tosyl derivative since the product gave no colour with ferric chloride and was soluble in sodium hydroxide but not in sodium hydrogen carbonate solution. Bromine water in slight excess gave a *dibromo-compound* (90%), colourless needles (from water), m. p. 210—214° (Found: C, 22·4; H, 1·7; N, 3·9. $C_6H_5O_3NSBr_2$ requires C, 21·8; H, 1·5; N, 4·2%).

Reaction of o-*acetoxybenzenesulphonyl chloride with ammonia.* *o*-Acetoxybenzenesulphonyl chloride [7] (20 g.) was kept in 40% aqueous ammonia for 2 days. The filtered mixture was evaporated on the steam-bath, and the residue digested with water and again evaporated. The oily residual solid was boiled with dilute aqueous sodium hydroxide, and the cooled solution acidified with sulphuric acid. Recrystallisation from water afforded a *compound*, m. p. 157—159° (Found: C, 43·1; H, 3·3; N, 4·3; S, 19·0. $C_{12}H_{11}O_6NS_2$ requires C, 43·8; H, 3·3; N, 4·25; S, 19·4%).

RESEARCH LABORATORIES, BOOTS PURE DRUG CO. LTD.,
NOTTINGHAM.

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[4] Raffa, *Il Farm.* (*Ed. Sci.*), 1956, **11**, 62.
[5] Limpricht, *Annalen*, 1875, **177**, 79.
[6] Sieglitz and Koch, *Ber.*, 1925, **58**, 79.
[7] Anschütz, *Annalen*, 1918, **415**, 69.

XUM

CONTENTS

General, physical, and inorganic

NO.		PAGE
599	Organometallic and organometalloidal fluorine compounds. Part XIV. Trifluoromethyl derivatives of selenium By J. W. Dale, H. J. Emeléus, and R. N. Haszeldine	2939
601	The phosphates of calcium. Part V. Revision of the earlier space diagram By Henry Bassett	2949
612	Studies in the pyrolysis of organic bromides. Part XI. The maximally inhibited rate of decomposition of *sec.*-butyl bromide By M. N. Kale, Allan Maccoll, and P. J. Thomas	3016
628	The vapour pressure of anhydrous copper nitrate, and its molecular weight in the vapour state By C. C. Addison and B. J. Hathaway	3099
632	Complex formation between ferric ion and glycine By D. D. Perrin	3120
633	The stability of complexes of ferric ion and amino-acids By D. D. Perrin	3125
635	The halides of niobium (columbium) and tantalum. Part V. Diethyl ether complexes of the pentachlorides and pentabromides; the solubility of tantalum pentaiodide in ether By Alan Cowley, Fred Fairbrother, and Norman Scott	3133
636	The infrared spectra of some simple and complex carbonates By B. M. Gatehouse, S. E. Livingstone, and R. S. Nyholm	3137
637	The ultraviolet absorption spectrum of dinitrogen tetroxide in organic solvents By C. C. Addison and J. C. Sheldon	3142
638	Tetracarbonyl halides of rhenium By E. W. Abel, G. B. Hargreaves, and G. Wilkinson	3149
649	The transmission of electronic effects through a palladium atom By J. Chatt, L. A. Duncanson, and L. M. Venanzi	3203
650	Vapour pressures of metal alkoxides. Part I. Titanium tetra-*tert.*-butoxide and -amyloxide By D. C. Bradley and J. D. Swanwick	3207
NOTES		
651	A new double spoon gauge By J. D. Swanwick	3214
653	The preparation and properties of some plutonium compounds. Part VIII. Plutonium(IV) sulphate By J. L. Drummond and G. A. Welch	3218
657	The solubility of anhydrous aluminium bromide in pent-2-ene By Fred Fairbrother and John F. Nixon	3224

Physical organic

594	The thermal decomposition of keten By J. R. Young	2909
598	The hydrolysis of simple amides catalysed by carboxylic acids By K. G. Wyness	2934
605	Potential purine antagonists. Part X. Purines and pyrazolopyrimidines: comparisons of ionisation By B. M. Lynch, R. K. Robins, and (in part) C. C. Cheng	2973

XUM

NO.		PAGE
610	Molecular polarisability. Application of the N–H and N–C link polarisabilities to the conformations of tertiary amines, piperidine, and morpholine By M. Aroney and R. J. W. Le Fèvre	3002
626	Electrophilic substitution. Part XII. The nitration of diphenylmethane, fluorene, diphenyl ether, dibenzofuran, diphenylamine, and carbazole; relative reactivities and partial rate factors By M. J. S. Dewar and D. S. Urch	3079
630	The titration and the apparent dissociation constants of weak acids in mixed aqueous solvents By M. K. Hargreaves and P. J. Richardson	3111
641	Infrared studies of heterocyclic compounds. Part III. 3-Monosubstituted pyridines By A. R. Katritzky, A. R. Hands, and R. A. Jones	3165
642	The effect of conformation on the rate of unimolecular solvolysis of aralkyl chlorides By G. Baddeley, J. W. Rasburn, and R. Rose	3168
643	Relation between hyperconjugation and conformation. Part II. The ethyl alcoholysis of some homologues of diphenylmethyl chloride By G. Baddeley, S. Varma, and (in part) M. Gordon	3171
646	Infrared spectra and the polymorphism of glycerides. Part IV. Myristo-palmitins and myristostearins By D. Chapman	3186

Notes

652	Vinylanthracenes, and the polymerization of the 9-isomer By Ernst D. Bergmann and Dov Katz	3216
659	Polyenealdehydes as proton acceptors By Albert Wassermann	3228
660	Deuteration of glyoxaline studied by nuclear magnetic resonance By R. J. Gillespie, A. Grimison, J. H. Ridd, and R. F. M. White	3228
662	The stereoisomers of 2 : 4-dimethyl-1 : 3-dioxolan By S. A. Barker, E. J. Bourne, R. M. Pinkard, M. Stacey, and D. H. Whiffen	3232

Organic

593	The mechanism of the reduction of some nicotinamide derivatives By Yehuda Paiss and Gabriel Stein	2905
595	The preparation of some esters of methyl 4 : 6-*O*-benzylidene-α-D-altroside By K. S. Ennor, John Honeyman, C. J. G. Shaw, and Theo. C. Stening	2921
596	The Fries rearrangement. Part V. Effect of the ring substituent and the acyl group By N. M. Cullinane and B. F. R. Edwards	2926
597	Griseofulvin. Part XIII. Homologues of griseofulvin and 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-ene-3 : 2′-dione By L. A. Duncanson, John Frederick Grove, and P. W. Jeffs	2929
600	Carcinogenic nitrogen compounds. Part XXV. Steric hindrance to cyclisation of 6-aminochrysene and its derivatives By G. C. Barrett and Ng. Ph. Buu-Hoï	2946
602	Reduced cyclic compounds. Part IV. The intramolecular acylation of some olefinic acids By M. F. Ansell and S. S. Brown	2955
603	The synthesis of cephalin (phosphatidylethanolamine) and batyl, chimyl, glycol, and alkyl analogues By R. L. Baylis, T. H. Bevan, and T. Malkin	2962
604	Studies on phosphorylation. Part XVII. The hydrolysis of methyl 3-(*OO*-dimethylphosphoryloxy)but-2-enoate By E. Y. Spencer, Sir Alexander Todd, and R. F. Webb	2968
606	Molecular rearrangements. Part II. 2 : 6-Disubstituted *N*-chloroacetanilides By C. Beard and W. J. Hickinbottom	2982

XUM

NO. PAGE

607 Picrotoxin. Part VII. The chemistry of anhydropicrotin
By J. S. E. Holker, Alexander Robertson, and J. H. Taylor, with (in part) K. U. Holker and W. R. N. Williamson 2987

608 Unsymmetrical dialkylphosphinic acids
By P. C. Crofts and I. S. Fox 2995

609 Submicro-methods for the analysis of organic compounds. Part IV. The determination of iodine and bromine
By R. Belcher, R. A. Shah, and T. S. West 2998

611 Condensations of the xylenols with carbon tetrahalides
By J. E. Driver and (Miss) T. F. Lai 3009

613 (±)-*allo*Yohimbone and (±)-3-*epialloy*ohimbone
By P. G. Philpott and A. M. Parsons 3018

614 Quinolizines. Part II. A synthesis of alkyl- and of aryl-quinolizinium salts
By E. E. Glover and Gurnos Jones 3021

615 Deoxynucleosides and related compounds. Part VI. The synthesis of 2-thiouridine and of 3′-deoxyuridine
By D. M. Brown, D. B. Parihar, Sir Alexander Todd, and S. Varadarajan . 3028

616 Deoxynucleosides and related compounds. Part VII. The synthesis of 2′-deoxyuridine and of thymidine
By D. M. Brown, D. B. Parihar, C. B. Reese, and Sir Alexander Todd. . 3035

617 Studies on phosphorylation. Part XVIII. Base-inhibited hydrogenolysis in the selective debenzylation of phosphoric and phosphoramidic esters
By V. M. Clark, G. W. Kirby, and Sir Alexander Todd 3039

618 Steric effects in 2 : 2′-bridged diphenyls with a heterocyclic bridging ring. Part I. Optically active dihydrodibenzazepines
By Shakti R. Ahmed and D. Muriel Hall 3043

619 Steroids and Walden inversion. Part XL. The configurations of the bromination products of androstan-17-one
By C. W. Shoppee, R. H. Jenkins, and G. H. R. Summers 3048

620 The reaction of 2-keto-carboxylic acids and esters with aromatic compounds in sulphuric acid
By Saul Patai and Shelomo Dayagi 3058

621 Some new analogues of pethidine. Part II. Alkoxyalkylnorpethidines
By P. M. Frearson and E. S. Stern 3062

622 Some new analogues of pethidine. Part III. 1-Aryloxyalkylnorpethidines, and close analogues
By P. M. Frearson and E. S. Stern 3065

623 Synthesis and properties of dehydropyridocolinium salts
By A. Richards and T. S. Stevens 3067

624 New heteroaromatic compounds. Part I. 9-Aza-10-boraphenanthrene
By M. J. S. Dewar, Ved P. Kubba, and R. Pettit 3073

625 New heteroaromatic compounds. Part II. Boron compounds isoconjugate with indole, 2 : 3-benzofuran, and thionaphthen
By M. J. S. Dewar, Ved P. Kubba, and R. Pettit 3076

627 The chemistry of the bile pigments. The structures of stercobilin and d-urobilin
By C. H. Gray and D. C. Nicholson 3085

629 Synthesis of cytidine diphosphate glycerol
By J. Baddiley, J. G. Buchanan, and A. R. Sanderson. 3107

631 The scope and mechanism of carbohydrate osotriazole formation. Part II. The action of oxidising agents on osazones and osotriazoles
By H. El Khadem and Zaki M. El-Shafei 3117

634 The preparation of optically active phosphorus compounds
By M. Green and R. F. Hudson 3129

639 Mechanism of the Kolbe–Schmitt reaction. Part II. Influence of the alkali metal
By S. E. Hunt, J. Idris Jones, A. S. Lindsey, and (in part) D. C. Killoh and H. S. Turner 3152

XUM

NO.		PAGE
640	Methylnicotinic acids. Part II By E. TITTENSOR and D. G. WIBBERLEY	3161
644	The constitution of the *leuco*anthocyanidin, peltogynol By W. R. CHAN, W. G. C. FORSYTH, and C. H. HASSALL	3174
645	Intermediates in the conversion of pinonic acid into carbocyclic compounds By C. L. ARCUS and G. J. BENNETT	3180
647	The structure of bornesitol By SHLOMO BIEN and DAVID GINSBURG	3189
648	Researches on acetylenic compounds. Part LXII. The interaction of amines and the stereoisomers of 5-chlorohex-3-en-1-yne By IAN BELL, R. MADROÑERO, and M. C. WHITING	3195

NOTES

654	Solvated triphenylmethane derivatives containing bromine By J. E. DRIVER and (MISS) T. F. LAI	3219
655	Properties and reactions of alkyl free radicals in solution. Part XI. Further water-soluble radicals By R. M. HAINES and WILLIAM A. WATERS	3221
656	Hydrogenation of 4-hydroxy*iso*phthalic acid By A. S. LINDSEY	3222
658	A new synthesis of clavatol and of sorbicillin By J. F. W. MCOMIE and M. S. TUTE	3226
661	New transformation products of nicotine By A. W. JOHNSON, T. J. KING, and J. R. TURNER	3230

INDEX OF AUTHORS' NAMES

ABEL, E. W., Hargreaves, G. B., and Wilkinson, G., 3149
Addison, C. C., and Hathaway, B. J., 3099
Addison, C. C., and Sheldon, J. C., 3142
Ahmed, S. R., and Hall, D. M., 3043
Ansell, M. F., and Brown, S. S., 2955
Arcus, C. L., and Bennett, G. J., 3180
Aroney, M., and Le Fèvre, R. J. W., 3002
Baddeley, G., Rasburn, J. W., and Rose, R., 3168
Baddeley, G., Varma, S., and Gordon, M., 3171
Baddiley, J., Buchanan, J. G., and Sanderson, A. R., 3107
Barker, S. A., Bourne, E. J., Pinkard, R. M., Stacey, M., and Whiffen, D. H., 3232
Barrett, G. C., and Buu-Hoï, Ng. Ph., 2946
Bassett, H., 2949
Baylis, R. L., Bevan, T. H., and Malkin, T., 2962
Beard, C., and Hickinbottom, W. J., 2982
Belcher, R., Shah, R. A., and West, T. S., 2998
Bell, I., Madroñero, R., and Whiting, M. C., 3195
Bennett, G. J. See Arcus, C. L., 3180
Bergmann, E. D., and Katz, D., 3216
Bevan, T. H. See Baylis, R. L., 2962
Bien, S., and Ginsburg, D., 3189
Bourne, E. J. See Barker, S. A., 3232
Bradley, D. C., and Swanwick, J. D., 3207
Brown, D. M., Parihar, D. B., Reese, C. B., and Todd, Sir A., 3035
Brown, D. M., Parihar, D. B., Todd, Sir A., and Varadarajan, S., 3028
Brown, S. S. See Ansell, M. F., 2955
Buchanan, J. G. See Baddiley, J., 3107
Buu-Hoï, Ng. Ph. See Barrett, G. C., 2946
Chan, W. R., Forsyth, W. G. C., and Hassall, C. H., 3174
Chapman, D., 3186
Chatt, J., Duncanson, L. A., and Venanzi, L. M., 3203
Cheng, C. C. See Lynch, B. M., 2973
Clark, V. M., Kirby, G. W., and Todd, Sir A., 3039
Cowley, A., Fairbrother, F., and Scott, N., 3133
Crofts, P. C., and Fox, I. S., 2995
Cullinane, N. M., and Edwards, B. F. R., 2926
Dale, J. W., Emeléus, H. J., and Haszeldine, R. N., 2939
Dayagi, S. See Patai, S., 3058
Dewar, M. J. S., Kubba, V. P., and Pettit, R., 3073, 3076
Dewar, M. J. S., and Urch, D. S., 3079
Driver, J. E., and Lai, T. F., 3009, 3219
Drummond, J. L., and Welch, G. A., 3218
Duncanson, L. A., Grove, JOHN FREDERICK, and Jeffs, P. W., 2929
Duncanson, L. A. See also Chatt, J., 3203
Edwards, B. F. R. See Cullinane, N. M., 2926
El Khadem, H., and El-Shafei, Z. M., 3117
El-Shafei, Z. M. See El Khadem, H., 3117
Emeléus, H. J. See Dale, J. W., 2939
Ennor, K. S., Honeyman, J., Shaw, C. J. G., and Stening, T. C., 2921
Fairbrother, F., and Nixon, J. F., 3224
Fairbrother, F. See also Cowley, A., 3133
Forsyth, W. G. C. See Chan, W. R., 3174
Fox, I. S. See Crofts, P. C., 2995
Frearson, P. M., and Stern, E. S., 3062, 3065
Gatehouse, B. M., Livingstone, S. E., and Nyholm, R. S., 3137
Gillespie, R. J., Grimison, A., Ridd, J. H., and White, R. F. M., 3228
Ginsburg, D. See Bien, S., 3189

Glover, E. E., and Jones, G., 3021
Gordon, M. See Baddeley, G., 3171
Gray, C. H., and Nicholson, D. C., 3085
Green, M., and Hudson, R. F., 3129
Grimison, A. See Gillespie, R. J., 3228
Grove, JOHN FREDERICK. See Duncanson, L. A., 2929
Haines, R. M., and Waters, W. A., 3221
Hall, D. M. See Ahmed, S. R., 3043
Hands, A. R. See Katritzky, A. R., 3165
Hargreaves, G. B. See Abel, E. W., 3149
Hargreaves, M. K., and Richardson, P. J., 3111
Hassall, C. H. See Chan, W. R., 3174
Haszeldine, R. N. See Dale, J. W., 2939
Hathaway, B. J. See Addison, C. C., 3099
Hickinbottom, W. J. See Beard, C., 2982
Holker, J. S. E., Robertson, A., Taylor, J. H., Holker, K. U., and Williamson, W. R. N., 2987
Holker, K. U. See Holker, J. S. E., 2987
Honeyman, J. See Ennor, K. S., 2921
Hudson, R. F. See Green, M., 3129
Hunt, S. E., Jones, J. I., Lindsey, A. S., Killoh, D. C., and Turner, H. S., 3152
Jeffs, P. W. See Duncanson, L. A., 2929
Jenkins, R. H. See Shoppee, C. W., 3048
Johnson, A. W., King, T. J., and Turner, J. R., 3230
Jones, G. See Glover, E. E., 3021
Jones, J. I. See Hunt, S. E., 3152
Jones, R. A. See Katritzky, A. R., 3165
Kale, M. N., Maccoll, A., and Thomas, P. J., 3016
Katritzky, A. R., Hands, A. R., and Jones, R. A., 3165
Katz, D. See Bergmann, E. D., 3216
Killoh, D. C. See Hunt, S. E., 3152
King, T. J. See Johnson, A. W., 3230
Kirby, G. W. See Clark, V. M., 3039
Kubba, V. P. See Dewar, M. J. S., 3073, 3076
Lai, T. F. See Driver, J. E., 3009, 3219
Le Fèvre, R. J. W. See Aroney, M., 3002
Lindsey, A. S., 3222
Lindsey, A. S. See also Hunt, S. E., 3152
Livingstone, S. E. See Gatehouse, B. M., 3137
Lynch, B. M., Robins, R. K., and Cheng, C. C., 2973
Maccoll, A. See Kale, M. N., 3016
McOmie, J. F. W., and Tute, M. S., 3226
Madroñero, R. See Bell, I., 3195
Malkin, T. See Baylis, R. L., 2962
Nicholson, D. C. See Gray, C. H., 3085
Nixon, J. F. See Fairbrother, F., 3224
Nyholm, R. S. See Gatehouse, B. M., 3137
Paiss, Y., and Stein, G., 2905
Parihar, D. B. See Brown, D. M., 3028, 3035
Parsons, A. M. See Philpott, P. G., 3018
Patai, S., and Dayagi, S., 3058
Perrin, D. D., 3120, 3125
Pettit, R. See Dewar, M. J. S., 3073, 3076
Philpott, P. G., and Parsons, A. M., 3018
Pinkard, R. M. See Barker, S. A., 3232
Rasburn, J. W. See Baddeley, G., 3168
Reese, C. B. See Brown, D. M., 3035
Richards, A., and Stevens, T. S., 3067
Richardson, P. J. See Hargreaves, M. K., 3111
Ridd, J. H. See Gillespie, R. J., 3228
Robertson, A. See Holker, J. S. E., 2987
Robins, R. K. See Lynch, B. M., 2973
Rose, R. See Baddeley, G., 3168
Sanderson, A. R. See Baddiley, J., 3107
Scott, N. See Cowley, A., 3133
Shah, R. A. See Belcher, R., 2998
Shaw, C. J. G. See Ennor, K. S., 2921
Sheldon, J. C. See Addison, C. C., 3142
Shoppee, C. W., Jenkins, R. H., and Summers, G. H. R., 3048
Spencer, E. Y., Todd, Sir A., and Webb, R. F., 2968
Stacey, M. See Barker, S. A., 3232
Stein, G. See Paiss, Y., 2905
Stening, T. C. See Ennor, K. S., 2921
Stern, E. S. See Frearson, P. M., 3062, 3065
Stevens, T. S. See Richards, A., 3067
Summers, G. H. R. See Shoppee, C. W., 3048
Swanwick, J. D., 3214
Swanwick, J. D. See also Bradley, D. C., 3207
Taylor, J. H. See Holker, J. S. E., 2987
Thomas, P. J. See Kale, M. N., 3016
Tittensor, E., and Wibberley, D. G., 3161
Todd, Sir A. See Brown, D. M., 3028, 3035, Clark, V. M., 3039, and Spencer, E. Y., 2968
Turner, H. S. See Hunt, S. E., 3152
Turner, J. R. See Johnson, A. W., 3230
Tute, M. S. See McOmie, J. F. W., 3226
Urch, D. S. See Dewar, M. J. S., 3079
Varadarajan, S. See Brown, D. M., 3028
Varma, S. See Baddeley, G., 3171
Venanzi, L. M. See Chatt, J., 3203
Wassermann, A., 3228
Waters, W. A. See Haines, R. M., 3221
Webb, R. F. See Spencer, E. Y., 2968
Welch, G. A. See Drummond, J. L., 3218
West, T. S. See Belcher, R., 2998
Whiffen, D. H. See Barker, S. A., 3232
White, R. F. M. See Gillespie, R. J., 3228
Whiting, M. C. See Bell, I., 3195
Wibberley, D. G. See Tittensor, E., 3161
Wilkinson, G. See Abel, E. W., 3149
Williamson, W. R. N. See Holker, J. S. E., 2987
Wyness, K. G., 2934
Young, J. R., 2909

XUM

PAPERS ACCEPTED

The conductivity of silver salts in non-aqueous and mixed solvents. Part VII. By V. S. Griffiths, K. S. Lawrence, and M. L. Pearce

A rapid method for the calculation of the molecular-orbital secular equation. By D. S. Urch

Adsorption on oxide gels from binary liquid mixtures: some surface-activity coefficients. By J. J. Kipling and D. B. Peakall

The synthesis of 5-iodotryptophan and some derivatives. By D. G. Harvey

A simple MO-LCAO method for the calculation of charge distributions in saturated organic molecules. By Giuseppe del Re

Tautomeric pyridines. Part I. Pyrid-2- and -4-thione. By R. A. Jones and A. R. Katritzky

High-temperature (300—350°) reactions of *cyclo*pentenone and some of its derivatives with ammonia and aliphatic amines. By O. B. Edgar and David H. Johnson

Germanium esters. Part II. Intermolecular forces and liquid structure. By D. C. Bradley, L. J. Kay, J. D. Swanwick, and W. Wardlaw

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Organophosphorus compounds of sulphur and selenium. Part X. Action of sulphuryl chloride on alkyl hydrogen alkylphosphonothioates and dialkylphosphinothioic acids. Synthesis of *P*-alkoxy-*P*-alkyloxophosphoranesulphenyl chlorides. By Cz. Borecki, J. Michalski, and St. Musierowicz

The chlorination and bromination of hydrocarbons under influence of high-energy radiation and other initiating agents. By R. A. Cox and A. J. Swallow

Technetium. Part I. The preparation and properties of the potassium hexahalogeno-technates. By J. Dalziel, N. A. Gill, R. S. Nyholm, and R. D. Peacock

Hydroxytryptamines. Part IV. Synthesis and reactions of 2-3′-oxindolylethylamines. By John Harley-Mason and R. F. J. Ingleby

A convenient solid for calibration of the Gouy magnetic susceptibility apparatus. By B. N. Figgis and R. S. Nyholm

The denitration of nitroguanidines in strong acids. Part I. The correlation of rate constants with the acidity function, H_0, and activities of solvent entities. By T. G. Bonner and J. C. Lockhart

The denitration of nitroguanidines in strong acids. Part II. Absorption spectra and pK_a values of certain nitroguanidines. By T. G. Bonner and J. C. Lockhart

The oxidation of proline, hydroxyproline, and *N*-methylglycine with periodate. By P. D. Bragg and L. Hough

Characterisation of thiols by means of their *p*-*p*′-nitrophenylazobenzoyl derivatives. By El S. Amin

Polycyclic systems. Part III. A synthesis of 1 : 2 : 9-trimethylpicene. By D. Nasipuri

Chalcones and related compounds. Part VII. Catalysed exchange of hydrogen cyanide between acetone cyanohydrin and chalcones. By B. E. Betts and W. Davey

The constitution of jute hemicellulose I. By G. O. Aspinall and P. C. Das Gupta

The magnetic properties of the quinquevalent complex fluorides of molybdenum, tungsten, and rhenium. By G. B. Hargreaves and R. D. Peacock

Electrometric titration of the sodium salts of deoxyribonucleic acids. Part VI. The forward-titration curve. By R. A. Cox and A. R. Peacocke

The activation of carbon–carbon double bonds by cationic catalysts. Part VI. The effect of substituents on the dimerisation of 1 : 1-diarylethylenes catalysed by trichloroacetic acid. By Alwyn G. Evans, Peter M. S. Jones, and J. H. Thomas

The preparation of 9α-fluoro-analogues of cortisol acetate and prednisolone acetate from 11 : 20-diketones. By J. Elks, G. H. Phillipps, and W. F. Wall

Oxidations with iodosobenzene diacetate. Part VIII. A kinetic study of the oxidation of benzpinacol. By L. K. Dyall and K. H. Pausacker

XUM

The effect of the nitro-group on the reactivity of the diphenyl nucleus in nitration. Competitive nitration of nitrodiphenyls and benzene by nitric acid in acetic anhydride. By Y. Mizuno and O. Simamura

The kinetics of hydrogen isotope exchange reactions. Part VIII. Hydrogen exchange between aromatic compounds and aqueous solutions of weak acids. Hammett's acidity function in such solutions. By D. P. N. Satchell

The reaction between aromatic compounds and derivatives of tertiary acids. Part XI. Friedel–Crafts reactions with optically-active acid. By William Bleazard and Eugene Rothstein

Polysaccharides of baker's yeast. Part II. Yeast glucan. By Stanley Peat, W. J. Whelan, and T. E. Edwards

Polysaccharides of baker's yeast. Part III. The presence of 1 : 6-linkages in yeast glucan. By Stanley Peat, J. R. Turvey, and J. H. Evans

The frequencies and intensities of the N–H stretching vibrations in primary amines. By S. F. Mason

The reduction of *N*-phenylhydroxylamine with lithium alumium hydride. By M. L. Burstall and M. S. Gibson

The cyclodehydration of anils. Part III. The alternative hydrolytic reaction. By T. G. Bonner and Mary Barnard

The cyclodehydration of anils. Part IV. Substituent effects. By T. G. Bonner and Mary Barnard

Metallic complexes of dimethyl *o*-methylthiophenylarsine. Part I. Complexes of nickel and palladium. By Stanley E. Livingstone

The infrared spectra and structures of some acyloxy-derivatives of boron. By L. A. Duncanson, W. Gerrard, M. F. Lappert, H. Pyszora, and R. Shafferman

Energy levels of planar diphenyl. By E. Theal Stewart

The melting points of *cis-* and *trans-cyclo*hexane-1 : 2-diol di-*p*-nitrobenzoates. By T. H. Elliott

The synthesis of flavan-2 : 3-diols (dihydro-α : 2-dihydroxychalcones). By J. W. Gramshaw, A. W. Johnson, and T. J. King

The synthesis of 4-aminopteridines as potential anti-metabolites. By C. L. Leese and G. M. Timmis

Potential anti-purines. Part II. The synthesis of 6- and 9-substituted purines and 8-aza-purines. By C. L. Leese and G. M. Timmis.

Synthesis of the 3-2′-aminopropyl- and 3-2′-aminobutyl- derivatives of 5-hydroxyindole, and an alternative synthesis of 5-hydroxytryptamine. By A. S. F. Ash and W. R. Wragg

Per-rhenyl fluoride. By E. E. Aynsley and M. L. Hair

The solvation of calcium nitrate and of lithium perchlorate in acetone solution measured by an ultrasonic method. By P. G. T. Fogg

Some properties of solid carbon monosulphide. By N. A. P. Hogg and J. E. Spice

16α-Carboxyprogesterone. By B. Ellis, V. Petrow, and (Miss) D. Wedlake

Structure of fulminate ion and pyrofulmin. By Kartar Singh

The reaction of organolithium compounds with some halogeno-acetals. By Gurnos Jones and H. D. Law

Isomerisation of phenylpropargylidenemalonic acid to γ-benzylidene-α-carboxybutenolide. By Juan Castañer and José Pascual

Extractives from the New Zealand Myrtaceae. Part III. Triterpene acids from the bark of *Leptospermum scoparium*. By R. E. Corbett and M. A. McDowall

The preparation of the five 2-methyl-*x*-phenylpentanes. By G. M. K. Hughes.

Volume changes on mixing organic liquids with dinitrogen tetroxide; comparison with sulphur dioxide systems. By C. C. Addison and B. C. Smith

The crystal structure of mercury dithizonate. By Marjorie M. Aitken

Indicator measurements and hydrogen isotope exchange in the solvent systems $SnCl_4$–CH_3CO_2H and $SnCl_4$–HCl–CH_3CO_2H. By D. P. N. Satchell.

Purines, pyrimidines, and glyoxalines. Part XI. Some oxazolidino- and thiazolidino-(2 : 3-*a*)-pyrimidines, and a synthesis of thymidine. By G. Shaw and R. N. Warrener.

The oxidation of aromatic amines. Part VII. The action of persulphate on some aromatic amines. By E. Boyland and Peter Sims

The synthesis of some benziminazoles. By R. M. Acheson, G. A. Taylor, and Muriel L. Tomlinson

Infrared spectra of uranyl nitrate hydrates and rubidium uranyl nitrate. By Bryan M. Gatehouse and Alan E. Comyns

Acid-stable organic azides, and the Schmidt reaction with heterocyclic ketones. By M. M. Coombs

XUM

Thiophen derivatives. Part XIII. Some reactions of 3-methylthiophen. By J. Lamy, Denise Lavit, and Ng Ph. Buu-Hoï

Carotenoids and related compounds. Part VI. Some conjugated polyene diketones, and their comparison with capsorubin. By C. K. Warren and B. C. L. Weedon

Carotenoids and related compounds. Part VII. Synthesis of canthaxanthin and echinenone. By C. K. Warren and B. C. L. Weedon

The benzoylation of substituted anilines in different solvents. By A. N. Bose and Sir Cyril Hinshelwood

Xanthones: cyclisation of 3′-substituted 2-carboxydiphenyl ethers. By A. A. Goldberg and A. H. Wragg

Reactivity of xanthones bearing 1- and 3-chloro-substituents towards nucleophilic reagents. By A. A. Goldberg and A. H. Wragg

Observations on the rearrangement of amine oxides. By A. H. Wragg, T. S. Stevens, and D. M. Ostle

The rearrangement of sulphinic esters. By A. H. Wragg, J. S. McFadyen, and T. S. Stevens

Thermodynamics of ion association. Part IV. Dissociation of the bisulphate ion. By V. S. K. Nair and G. H. Nancollas

Thermodynamics of ion association. Part V. Magnesium and zinc sulphates. By V. S. K. Nair and G. H. Nancollas

The preparation of 7- and 9-ribofuranosyl derivatives of 8-azaxanthine. A note on the preparation of 9-glucopyranosylxanthine. By J. Baddiley, J. G. Buchanan, and G. O. Osborne

The condensation of 4 : 5-diaminopyrimidines and sugar lactones. By R. Hull.

The reaction between 3-chloro-3-methylbutyne and methyl sodioacetoacetate. By L. Crombie and K. Mackenzie

Calculated bond lengths in some cyclic compounds. Part V. 1 : 2–7 : 8–13 : 14-tribenzo*cyclo*octadeca-1 : 7 : 13-triene-3 : 5 : 9 : 11 : 15 : 17-hexayne and diphenyldiacetylene. By T. H. Goodwin

The structure and synthesis of bullatenone. By W. Parker, R. A. Raphael, and D. I. Wilkinson

Bis*cyclo*pentadienyl rhenium hydride. By M. L. H. Green, L. Pratt, and G. Wilkinson

The virial coefficients of *cyclo*hexane, carbon disulphide, and carbon tetrachloride vapours. By G. A. Bottomley and T. A. Remmington

The virial coefficients of carbon disulphide, diethyl ether, and *n*-hexane. By G. A. Bottomley and C. G. Reeves

Hydrothermal chemistry of the silicates. Part VIII. Low-temperature crystal growth of aluminosilicates, and of some gallium and geranium analogues. By R. M. Barrer, J. W. Baynham, F. W. Bultitude, and W. M. Meier

The polonium nitrates. By K. W. Bagnall, D. S. Robertson, and M. A. A. Stewart

Reactions with asymmetric di-arylethylenes. Part V. Conversion of 2 : 2-di-*p*-alkoxyphenylvinyl chloride or bromide in alkaline medium into the corresponding tolane. By Wadie Tadros, Alfy Badie Sakla, and Moheb Sadek Ishak

The indole alkaloids. Part II. Vobtusine and voacangine from *Voacanga dregei*. By B. O. G. Schuler, A. A. Verbeek, and F. L. Warren

The vapour pressures of nitric acid solutions. Part III. The deuterium oxide–dinitrogen pentoxide system. By J. G. Dawber and P. A. H. Wyatt

Deoxynucleosides and related compounds. Part VIII. Some further transformations of O^2 : 2′-*cyclo*uridine. By D. M. Brown, D. B. Parihar, and Sir Alexander Todd

1-Ethyl-3-methyl*cyclo*pentadiene. By D. A. H. Taylor

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Stereochemistry of metals of sub-group B. Part 1. Ions with filled *d*-electron shells. By L. E. Orgel

XUM

593. *The Mechanism of the Reduction of Some Nicotinamide Derivatives.*

By Yehuda Paiss and Gabriel Stein.

The electrolytic reduction of *N*-propylnicotinamide, proceeding by a mechanism involving one-electron transfer and free-radical intermediates, results in the formation of a dimer and a dihydro-compound. This dihydro-derivative differs from that produced by reduction with dithionite, which involves addition of a negative ion and two-electron transfer. Sodium borohydride yields a mixture of the two dihydro-derivatives, either of which may then be isolated at will.

N-Substituted nicotinamide derivatives are in many respects suitable models for the study of the mechanism of reduction of DPN^+ (coenzyme-I). They were studied by Karrer *et al.*,[1] who showed that reduction of nicotinamide propiodide by sodium dithionite gives a dihydro-compound which resembles DPNH in its properties. Colowick [2] and Swallow [3] have shown that the reduction is the result of a one-step, two-electron-equivalent transfer due to addition of a negative ion. Reduction of the coenzyme by dithionite yields an enzymically active product. Enzymic reduction involves transfer of a hydride ion.[4]

When *N*-substituted nicotinamides are reduced by free radicals, produced by irradiating the solutions with *X*- or γ-rays,[5] the product, a dihydro-compound, is not identical with the product of dithionite reduction. It was also shown that reduction by sodium borohydride [6] yielded a mixture of the two dihydro-compounds, which could be separated. Electrolytic reduction [6] produced the dihydronicotinamide also obtained from the irradiated solution. Similar results, in the case of borohydride, were obtained by Wallenfels and Schuly.[7] However the results were questioned by Karrer and his co-workers [8] who obtained by borohydride reduction only one dihydro-derivative, that resulting from dithionite reduction.

In the present paper it is shown that the absence of the other compound in Karrer's work is due to the experimental conditions employed. Conditions are now described which enable one to obtain either of the products, using borohydride. By the electrolyte method a dimer can also be isolated, in agreement with the postulated one-electron-transfer mechanism.

Experimental

Materials.—Sodium borohydride was obtained from B.D.H. Ltd., sodium dithionite from J. T. Baker Co. Nicotinamide methiodide, propiodide, and benzylochloride were prepared by the methods of Karrer's school.[1,8]

Spectra.—Ultraviolet spectra (see Figs.) were taken on a Beckman DU instrument. Fluorescence spectra were obtained on the same instrument fitted with the Beckman Special Fluorescence attachment, and Spectral Energy Recording Attachment. Infrared spectra were taken on a Baird double-beam instrument, in KBr discs.

Oxidative Titrations.—The solution was adjusted to pH 8—9 with borate buffer, and excess of 10^{-2}N-potassium ferricyanide solution in borate buffer (pH 8) was added. After 30 min.

[1] (*a*) Karrer, Schwarzenbach, Benz, and Solmssen, *Helv. Chim. Acta*, 1936, **19**, 811; (*b*) Karrer and Stare, *ibid.*, 1937, **20**, 418.
[2] Colowick, in "Mechanism of Enzyme Action," Johns Hopkins Press, Baltimore, 1954, p. 353; Yarmolinsky and Colowick, *Biochem. Biophys. Acta*, 1956, **20**, 177.
[3] Swallow, *Biochem. J.*, 1955, **60**, 443.
[4] Vennesland and Westheimer, in "Mechanism of Enzyme Action," Johns Hopkins Press, Baltimore, 1954, p. 357; Mahler and Douglas, *J. Amer. Chem. Soc.*, 1957, **79**, 1159.
[5] Stein and Swallow, *Nature*, 1954, **173**, 937; Stein, *J. Chim. phys.*, 1955, **52**, 634.
[6] Stein and Stiassny, *Nature*, 1955, **176**, 734.
[7] Wallenfels and Schuly, *Angew. Chem.*, 1955, **67**, 517.
[8] Brook, Blumer, Krishna, Schnell, and Karrer, *Helv. Chim. Acta*, 1956, **39**, 667.

XUM

2 ml. of 10% potassium iodide solution were added, followed by 2 ml. of 10% zinc sulphate solution and 3 ml. of 5N-hydrochloric acid. The iodide liberated was titrated with 10^{-2}N-thiosulphate. The same procedure was always carried out at the same time on a control solution.

Reduction by Sodium Dithionite.—This was carried out essentially according to the procedure of Karrer *et al.*[1] The propiodide (1 g.) was dissolved in M-sodium carbonate (20 ml.) at 0°. Whilst nitrogen was passed through the reaction mixture, small portions of solid dithionite were added. An orange colour appeared, fading to yellow. When further addition caused no further orange coloration the solution was extracted with peroxide-free ether (5 × 50 ml.). The ether extract was dried (Na_2SO_4) and distilled in the cold in vacuum until turbidity appeared. Addition of light petroleum (b. p. 40—60°, 5 ml.) precipitated crystals. Recrystallised from ether–light petroleum these had m. p. 92° (Found: C, 65·0; H, 8·4. Calc. for $C_9H_{14}ON_2$: C, 65·1; H, 8·4%). Oxidative titrations showed a mean value of 95% of the calculated. The absorption spectrum for an ether solution showed one maximum only, at 346 mμ (ε 5800). For aqueous carbonate solution the maximum is at 360 mμ. On addition of acid this peak disappears and a single new peak at 295 mμ appears. The maxima of the fluorescence spectrum lie at 430 mμ for ether and 480 mμ for 0·1M-sodium carbonate solution. We denote this product as dihydro-compound A.

Reduction by Sodium Borohydride.—The same procedure was used as with dithionite. The ether extract of the reaction mixture was dried (Na_2SO_4) and evaporated in a vacuum in the cold until turbidity appeared. The closed vessel was kept at −5°, till crystals were deposited; these had m. p. 103°, unchanged by recrystallisation. For ether solutions the spectrum

FIG. 1. *Absorption spectrum of dihydro-compound A (dashes) and B (solid curve).*

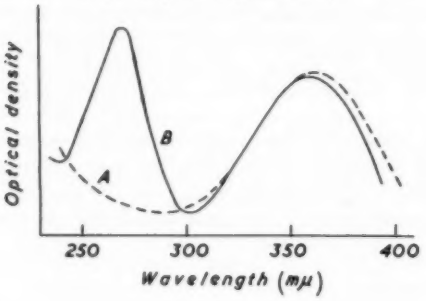
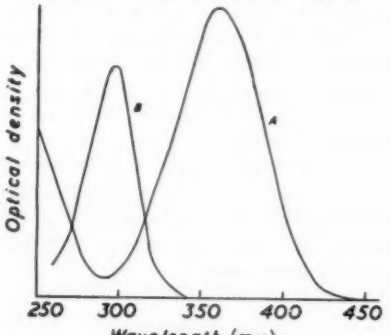


FIG. 2. *Absorption spectrum of dimer obtained by electrolytic reduction of nicotinamide propiodide* (3 × 10^{-2}M) in 0·1M-Na_2CO_3.



A, at pH 9. *B, at* pH 5.

(Fig. 1) has two peaks, at 265 and 350 mμ. At 350 mμ (ε 6700). The fluorescence spectrum shows one peak only at 443 mμ for ether and at 505 mμ for 0·1M-sodium carbonate solution. Oxidative titrations showed 95—98% of the theoretical value calculated for a dihydro-derivative. In the ether extract, after deposition of the crystals the spectrum exhibits both peaks, that at 350 mμ being the higher. If the solution of the new dihydro-derivative (B) in carbonate is acidified, both absorption peaks disappear and a single peak at 295 mμ appears, as with the product A.

For the preparation of B small quantities of nicotinamide propiodide and sodium borohydride were added alternately to N-sodium carbonate (3 ml.) at 0°. Borohydride was added after each addition of the substrate until no more orange colour was formed. Altogether 2 g. of starting material were used. Towards the end of the reaction the crystalline derivative B was precipitated. Recrystallised from warm water it had m. p. 103° (yield approx. 50%) (Found: C, 65·1; H, 8·25%).

Effect of Added Anions.—A few qualitative experiments were carried out on the rôle of the valency of added anions. If instead of sodium carbonate being used, the reaction solution was

adjusted to pH 11 by M-boric acid–sodium hydroxide buffer (H_3BO_3 being assumed effectively univalent at this pH), no crystalline product B was obtained, but an oil, which showed a spectrum indicating that it contained mainly A. If 0·1N-sodium carbonate was used, no crystalline product B was precipitated, but if 0·9N-sodium sulphate was also present, crystalline product B was obtained. If the sulphate was replaced by 0·9N-sodium chloride, no crystalline product B was precipitated.

Electrolytic Reduction.—This was carried out in a vessel having two mercury pools (anode and cathode), the catholyte volume being approx. 200 ml. The anolyte was 0·1M-sodium carbonate. Anode and cathode compartments were separated by 2% agar gel in saturated potassium chloride solution. The sealed-in current-carrying platinum electrodes were fully covered by the mercury. Both electrode compartments could be flushed with nitrogen. Ground-in fittings in the cathode compartment carried an auxiliary capillary agar bridge close to the mercury surface, to measure the cathode potential, and a syphon, using excess nitrogen pressure to withdraw samples directly into quartz spectrophotometer cells fitted with ground joints.

The catholyte was vigorously stirred at the surface of the mercury pool by a Teflon sealed magnetic stirrer. All preparations were carried out at a current of 1A and cathode area of approx. 30 cm.^{2}. The cathode potential was 0·3 V with reference to the standard calomel electrode before application of the electrolysing voltage, rising to −0·9 V at the beginning of the electrolysis which was continued until the electrode potential rose to −1·1 V. The current efficiency was approx. 30%, as determined by oxidative titration of the resultant solution.

Electrolytic Reduction of Nicotinamide Propiodide.—For 2×10^{-3}M-solutions, the optical density at 265 and 360 mμ increases during electrolysis, the ratio of the two optical densities remaining approximately constant. The product was assumed to be dihydro-derivative B and its concentration was calculated from the molar extinction coefficient. Oxidative titration of the electrolyte solution gave values which were 95% of the calculated. In other experiments the initial concentration was increased to 3×10^{-2}M, and electrolysed with a current of 1 A, with the cathode potential rising from −0·9 to −1·1 V. This cathode potential remained almost constant when the current was varied between 0·5 and 1·5 A. Under these conditions crystals (C) (15%) were formed. The solution was found by titration to contain approx. 85% of the starting material, calculated as the dihydro-derivative. The concentration calculated from the spectrum of the electrolyte solution agreed with this, if the absorption was assumed to be due to the dihydro-derivative B.

The crystals C (Found: C, 65·5; H, 7·7. Calc. for $C_{18}H_{26}O_2N_4$: C, 65·45; H, 7·9%) were easily soluble in ethanol, soluble in hot water and with difficulty in ether or cold water. It recrystallised from carbon dioxide-free hot water as lemon-coloured needles, m. p. 180° (decomp.). The absorption spectrum of a 0·1N-sodium carbonate solution exhibits one peak only, at 355 mμ (ε 10,600, *i.e.*, 5300 per nicotinamide unit of *M* 165). For an ether solution there is a similar spectrum, with the maximum at 345 mμ (owing to the low solubility ε could not be determined). On addition of acid the peak at 355 mμ disappears and a peak at 295 mμ appears. A weighed quantity of the material was dissolved in a small amount of ethanol, diluted with aqueous buffer, and titrated with ferricyanide: the material had 1 reducing equivalent per nicotinamide unit. Calculated on the assumption that the product is a dimer, the titrations gave results between 95 and 102% of the calculated value. The substance is not fluorescent in the solid state or in aqueous carbonate, ethanol, or ether. On acidification of its solution in aqueous carbonate the peak at 355 mμ disappears and a peak at 295 mμ appears.

2×10^{-3}M-Solutions of nicotinamide methiodide and benzylochloride were also reduced electrolytically. Product B was formed.

Infrared Spectra.—These were obtained for all three products in KBr discs and for derivative B in Nujol. For the derivatives A and B the spectra are very similar, no main bands exclusive to either occurring, although the relative intensities of several bands differ considerably. The spectrum of the dimer resembles that of the dihydro-derivatives, having in addition a band at 1025 cm.$^{-1}$.

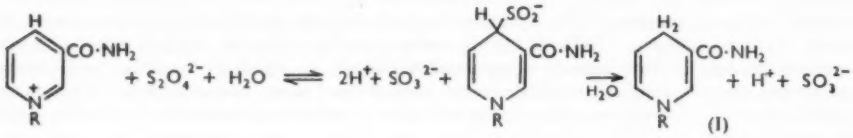
Discussion

The formation of the different products can be understood if we assume that one-electron-equivalent transfers yield free-radical intermediates, the final products differing

XUM

from those obtained by processes where two electron-equivalents are simultaneously transferred.

The reduction with dithionite yields the dihydro-derivative A first characterised by Karrer *et al.*[1] Colowick [2] and Swallow [3] have shown that a free-radical intermediate is not formed in this process. The orange intermediate colour is due to a complex formed by the addition of a negative ion, so that the reduction involves a single-step two-electron-equivalent reduction: [2]



Vennesland and Westheimer [4] showed that in the enzymic reduction of DPN^+ a proton is transferred directly from the substrate to the coenzyme, presumably as a hydride ion containing two electron-equivalents. The reduction of DPN^+ by dithionite also affords enzymically active DPNH. Colowick's work makes it likely that product A obtained by dithionite reduction is the *para*-derivative (I).

Reduction by sodium borohydride may yield the same dihydro-derivative A under the conditions described by Brook *et al.*[8] However, as the experimental conditions are modified another dihydro-derivative, B, is obtained. Mathews and Conn [9] found for DPN^+ that reduction with borohydride yields a product which is only partly enzymically active. The evidence in the present paper—its relatively low m. p., similar to that of A, its ultraviolet fluorescent and infrared spectrum, elementary analysis, and oxidation equivalents determined by titration—indicates that product B is another (*ortho*-)dihydro-derivative.

Regarding the mechanism of formation, it is significant that product B is formed in two other processes, whose mechanism involves a free-radical intermediate and involving single-electron-equivalent reduction steps. It was thus first observed when solutions of nicotinamide propiochloride in aqueous solutions of pH 8 containing added ethanol were irradiated with penetrating radiations (X- or γ-rays),[5] where it was shown that the reducing agent is the free radical derived from ethanol.

The same dihydro-compound B is obtained in the electrolytic reduction, which proceeds also by single-electron-equivalent transfer steps. Leach *et al.*[10] studied the electrolytic reduction of such model compounds of DPN^+, assuming the products to correspond to that obtained in dithionite (corresponding to enzymic) reduction. However, during electrolysis product B is formed. This agrees with the work of Bacon Ke [11] on the electrolytic reduction of DPN^+ at a mercury cathode. He showed that the product is enzymically inactive, and thus different from the product of dithionite or enzymic reduction.

Product B is thus formed in two different cases where single-electron-equivalent transfer steps, resulting in free-radical intermediates, operate. This suggests that borohydride too is capable under suitable conditions of acting partly by a single-electron transfer.

In a process involving free-radical intermediates, the radicals may disproportionate or dimerise. The isolation of the dimer (C) on electrolytic reduction supports the postulated single-electron-transfer mechanism and intermediate free radicals. Its spectrum makes it probable that it is the *para*-derivative. Increasing the concentration of the starting

[9] Mathews and Conn, *J. Amer. Chem. Soc.*, 1953, **75**, 5428.
[10] Leach, Baxendale, and Evans, *Austral. J. Chem.*, 1953, **6**, 395; Leach, *Adv. Enzymol.*, 1954, **15**, 1.
[11] Bacon Ke, *Arch. Biochem. Biophys.*, 1956, **60**, 505; *J. Amer. Chem. Soc.*, 1956, **78**, 3649.

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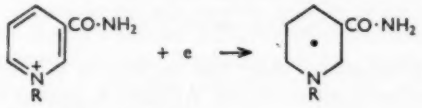
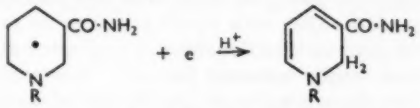
material favours dimer formation in the electrolytic reduction of nicotinamide propiodide. If in the first step at the electrode the radical is formed:



this may be followed at the electrode by:



i.e., formation of product B. If, however, the concentration of starting material is increased, these will be preferentially reduced at the electrode, leaving the radicals free to interact partly by dimerisation.

We thank Mr. Y. Steinberg for valuable help.

Department of Physical Chemistry, Hebrew University, Jerusalem, Israel. [*Received, September 23rd*, 1957.]

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594. *The Thermal Decomposition of Keten.*

By J. R. Young.

Keten has been pyrolysed in silica at *ca.* 100 mm. and 510—590°, reaction being followed by direct analysis of products. Disappearance of keten followed a second-order law. Consideration of the curves of formation of products and, in particular, the CO_2 : CO ratio leads to the tentative conclusion that the first stages of the reaction mechanism are:

$$2CH_2{:}CO \longrightarrow CH_2{:}C{:}CH_2 + CO_2$$
$$CH_2{:}C{:}CH_2 \longrightarrow C_2H_2 + {:}CH_2$$
$${:}CH_2 + CH_2{:}CO \longrightarrow {\cdot}CH_3 + {\cdot}CH{:}CO$$

which are followed by the attack of the methyl radical and probably of the $CH{:}$ radical (from breakdown of $\cdot CH{:}CO$) on keten. The chain length of the later stages increases with temperature, and the chain process may overwhelm the bimolecular breakdown at high temperatures.

Three previous investigations of the thermal decomposition of keten have given contradictory results. Williamson [1] concluded that in the temperature range 500—550° it was a unimolecular decomposition complicated by a simultaneous dimerisation which accounted for an initial fall in pressure at low temperatures. His final analysis of products (CO ~66%, CH_4 30%, C_2H_4 3·0%) disagreed with that found by Muller and Peytral [2] at 1120° (CO 66%, CH_4 10%, C_2H_4 22%). The larger ratio of ethylene to methane found by Muller and Peytral might be due to a change of mechanism at the higher temperature. However, the third study, by Akeroyd,[3] yielded results which conflict with the earlier work: a typical analysis of Akeroyd's products at 570° was CO 52%, CO_2 23%, CH_4 16%, and C_2H_4 9%, where the appearance of carbon dioxide is a new feature. Akeroyd

[1] Williamson, *J. Amer. Chem. Soc.*, 1930, **54**, 2216.
[2] Muller and Peytral, *Compt. rend.*, 1933, **196**, 379.
[3] Akeroyd, Ph.D. Thesis, Cambridge, 1936.

XUM

interpreted his results in terms of a unimolecular breakdown (1) supplemented by a bimolecular reaction (2):

$$CH_2{:}CO \longrightarrow {\cdot}CH_2{\cdot} + CO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$2CH_2{:}CO \longrightarrow CH_2{:}C{:}CH_2 + CO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Apart from the detail of the second stage this mechanism is kinetically compatible with Williamson's results, and both Akeroyd and Williamson proposed a kinetic order of 3/2 in keten.

In the present investigation pyrolyses have been carried out in a static system at temperatures in the range 510—570°, with initial pressures up to 300 mm. The kinetic results were obtained from periodic direct analyses of products and thus avoid errors which can be shown to arise from simply following pressure. Gas analyses were made by gas chromatography, which was also applied to the purification of the keten used.

Experimental

Preparation of Keten.—Acetone was refluxed over an electrically heated filament in a " keten lamp ".[4] The gases produced were cooled in three stages, a condensate at 20° was returned to the boiling-flask, a second (at −80°), which was a concentrated solution of keten in acetone, was rejected, and a third (at −195°) was worked up for keten. The amount of this condensate was relatively small but it contained very little acetone, which assisted subsequent purification. This was carried out by trap-to-trap distillation at successively −185°, −145°, −80°, and −80°. The keten remained in the residue in all stages except the third where it was separated from residual acetone. In the final stage the vapour was frequently chromatographically analysed until pure.

The yield (*ca.* 4% overall) on the final stage of this operation is largely determined by the difficulty of freeing the residual keten from propene and acetylene, which although initially present in small amounts become concentrated into the penultimate distillate. The keten finally prepared was consistently 98·5% pure and was stored under liquid nitrogen, the contaminants being propene *ca.* 1·2% and acetylene 0·3%; a higher purity would require column distillation. The vapour analyses made during the final operation showed that small amounts of material containing up to 20% of these impurities could be collected as intermediate fractions.

Kinetic Measurements.—The apparatus used for injection and removal of the sample or for following the pressure is shown in Fig. 1. The furnace was constructed from heat-resistant stainless-steel pipe of 3½" bore and ½" wall, with flanged ends. This was electrically heated and had a zone of uniform temperature sufficiently large to contain the silica reaction bulb (capacity 114 ml.). When this was run from a constant-voltage source the temperature stability was within ±0·25° for short periods and the day-to-day variation was not much greater.

At the commencement of each experiment the whole apparatus was evacuated to *ca.* 10^{-5} mm. for ½ hr. With the reaction bulb shut off at the three-way tap T_1, keten was admitted from *A* to the measuring bulb *B* which was also connected to the mercury manometer. Tap T_2 was then closed, trapping a sample at room temperature in the calibrated volume (137·5 ml.) between taps T_2 and T_6. Tap T_5 was next closed and the connecting tubes pumped free from keten before reversal of tap T_1 to connect the reaction bulb *C* with the manometer. Taps T_6 and T_2 were then opened and the sample was rapidly pushed by the rising mercury, through the sintered seal *D*, into the reaction bulb *C*. The pressure change was followed either manually or with an automatic device.[5] Samples were taken by admitting the reaction mixture to a Ward–Leroy still[6] *E*, cooled to −195°, *via* taps T_1 and T_4, etc., causing virtually instantaneous condensation of all products other than methane and carbon monoxide. The still was used in the normal way to fractionate the products and, in general, three fractions were removed, *viz.*, at −195° hydrogen, carbon monoxide, and methane (F_1), at −150° ethylene and ethane (F_2), and at −80° carbon dioxide, keten, propene and traces of C_4 hydrocarbons (F_3). Each fraction was transferred *via* a Töpler pump to the gas burette attached to the chromatography-column

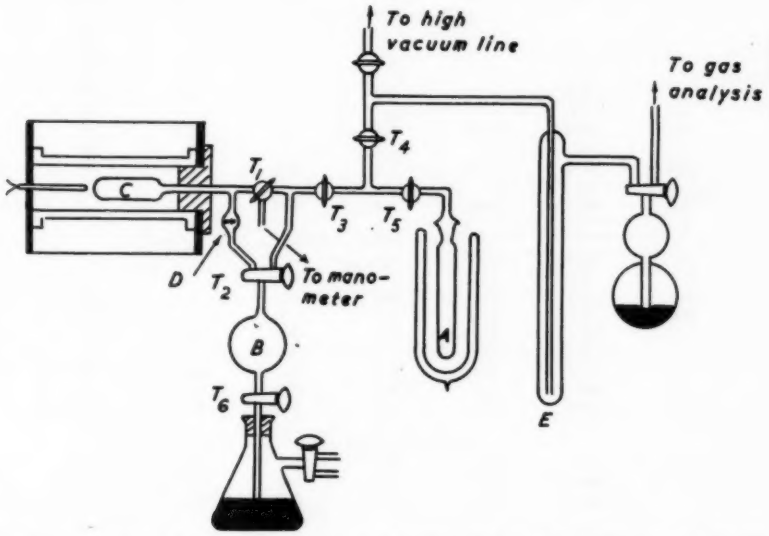
[4] Hurd, *Org. Synth.*, Col. Vol. I, 1932, p. 324.
[5] Young, *Chem. and Ind.*, in the press.
[6] Leroy, *Canad. J. Res.*, 1950, **28**, *B*, 492.

XUM

inlet. After measurement of its volume, the sample was injected directly into the carrier gas stream and conducted through the appropriate column.

Chromatographic Analysis.—Three columns were used for the complete analysis: column 1, containing 14 g. of active charcoal at 70°, was used for fraction F_1, giving carbon monoxide and methane directly and hydrogen by difference (however, when nitrogen was used as carrier gas all three gases were determined); column 2 containing 11·6 g. of active charcoal at 160° was used for fractions F_2 and F_3, but recorded carbon dioxide only when used for fraction F_3; column 3 containing 10 g. of dinonyl phthalate on 24 g. of Celite 505 separated fraction F_3 and recorded all components. In most cases fraction F_3 was analysed on column 2, giving carbon dioxide directly and keten by difference; occasional analysis of samples on column 3 gave a

FIG. 1.



quantitative measure of keten and allene. A detector of thermal-conductivity type similar to that described by Brooke, Murray, and Williams [7] was used: when thermally insulated this was stable and free from drift; at a chart speed of 1″ per min., with 1″ on the recorder scale = 1 mv and 150 ma bridge current, sensitivities between 12·0 and 4·7 cm.³/ml. at N.T.P. were obtained, depending on the standard operating conditions. Plots of peak area against sample volume plots were linear and the analytical accuracy was $\pm \sim 1{\cdot}5\%$ when estimated from the spread of the calibration plots.

A typical set of results is given in the table. The reproducibility of such analyses was good and variation on individual products rarely exceeded $\pm 5\%$ of the amount present.

Reaction conditions: 570°, $P_0 = 150$ mm. (7·84 ml. of keten at N.T.P.); 5 min. reaction time.

Volume of fractions: F_1 4·75, F_2 0·74, F_3 1·89 ml. (N.T.P.).

	H_2	CO	CH_4	C_2H_4	C_2H_6	CO_2	$CH_2{:}CO$
Peak areas (cm.²) ...	—	42·8	11·2	2·4	1·0	6·1	—
ml. (N.T.P.)	0·23	3·56	0·96	0·49	1·21	1·26	0·63
Mean of 4 runs	0·29	3·54	0·91	0·47	0·26	1·23	0·68

H_2 and $CH_2{:}CO$ are by difference.

The Ward–Leroy still gave clean separation of the products as long as the total charge was small. The maximum permissible charge was not determined but was probably about 25 ml.

[7] Brooke, Murray, and Williams, in Desty's "Chromatography," Butterworth, London, 1957, p. 333.

XUM

(N.T.P.) of mixture. If larger samples were used, particularly if these contained a high proportion of involatile material, fraction F_3 invariably contained traces of C_2 hydrocarbons indicating incomplete separation.

Identification of Allene.—The final fraction from the still, F_3, normally contained carbon dioxide and keten with several minor peaks following that of keten. The emergence times of these additional products from column 3 (standard conditions) are given below under the

TABLE 1. *Product analyses for keten pyrolysis at* 511°, *expressed as moles* % *on initial reactant.*

Reaction time (min.)	H_2 (diff.)	CO	CH_4	C_2H_4	C_2H_6	CO_2	Allene	Keten (diff.)
				At $P_0 = 280 \pm 2$ *mm.*				
¼	—	—	—	—	—	—	2·3	—
½	—	—	—	—	—	—	4·1	—
¾	—	—	—	—	—	—	5·4	—
1	0·2	8·0	0·5	1·1	—	8·0	5·6	69·8
1½	—	—	—	—	—	—	5·7	—
2	1·1	14·6	1·2	2·1	0·2	12·8	5·1	55·7
4	—	—	—	—	—	—	2·5	—
5	2·0	31·4	4·5	3·9	0·4	17·5	—	30·1
6	—	—	—	—	—	—	1·4	—
15	2·8	42·1	8·6	4·4	0·9	19·7	—	14·9
				At $P_0 = 140 \pm 1$ *mm.*				
¼	—	0·4	—	—	—	—	1·5	—
½	—	1·1	—	—	—	—	2·7	—
1	—	3·1	0·4	1·0	0·3	5·0	4·9	80·3
2	0·1	7·1	0·6	1·1	0·1	7·6	6·7	73·0
4	—	14·7	1·5	2·1	0·3	12·7	4·3	58·7
6	—	—	—	—	—	—	2·1	—
7	1·7	26·2	3·2	3·4	1·1	16·7	1·0	41·1
12	2·1	38·7	7·3	3·7	0·9	17·9	—	26·5
25	2·6	47·0	9·6	5·2	1·0	26·2	—	17·5
				At $P_0 = 70 \pm 1$ *mm.*				
7	—	24·6	3·0	3·7	0·7	12·8	—	55·1
15	—	30·2	4·9	4·7	0·6	14·1	—	40·0
25	—	43·2	8·2	5·6	0·9	15·4	—	28·2

headings A—F. Compound A occurred in greatest quantity and passed through a maximum during the early stages of reaction. Some of this compound was separated from a number of analyses: its infrared spectrum identified it as allene. The peaks B—F were not identified but from their emergence times it is probable that they are C_4—C_6 hydrocarbons.

Compound	$C_3H_4 + C_3H_6$	C_2H_2	C_2H_6	$CH_2{:}CO$	A	B	C	D	E	F
Elution time (sec.)	54	110	138	174	241	300	350	550	1100	1650

Since pure allene was not prepared it was estimated by assuming that its area sensitivity was the same as that found for propene. The curves for production of allene are shown in Fig. 6.

Results.—The pyrolysis was studied at five temperatures between 570° and 510°. At each, pressure–time curves were plotted and analytical kinetic runs were carried out for various initial pressures between 70 and 300 mm. In a few instances the pressure–time curves showed an initial fall which decreased through successive runs. In order to detect any variation in product ratio accompanying this effect, 3—5 analytical runs were made for each set of conditions, always first with a " burnt-out " reaction bulb. No significant differences were found between successive analyses and in the following the mean results are reported. Table 1 exemplifies the results at a single temperature.

The results obtained at 140 mm. and 511° are plotted in Figs. 2 and 3. The general features revealed in these figures were reproduced under all other conditions of pressure and temperature. We remark: (i) The keten decomposed is equal (within experimental error) to ($2CO_2$ + CO). (ii) The initial rate of formation of carbon dioxide is similar to that of allene formation and greater than that of carbon monoxide formation, though the latter inequality is reversed after *ca.* 35% decomposition. (iii) Formation rates for ethylene and methane show similar

XUM

behaviour to those for carbon dioxide and carbon monoxide respectively. (iv) Ethane and hydrogen are relatively unimportant products, and allene behaves as an unstable intermediate product. (v) The progress of the decomposition of keten is adequately described by a second-order rate equation.

Plots of time against the reciprocal of the keten pressure show a slope which is independent of the initial pressure within the range studied. Fig. 3 shows such plots for the data of Table 1

FIG. 2. *Product–time curves for pyrolysis of keten at 511° and 140 mm.*

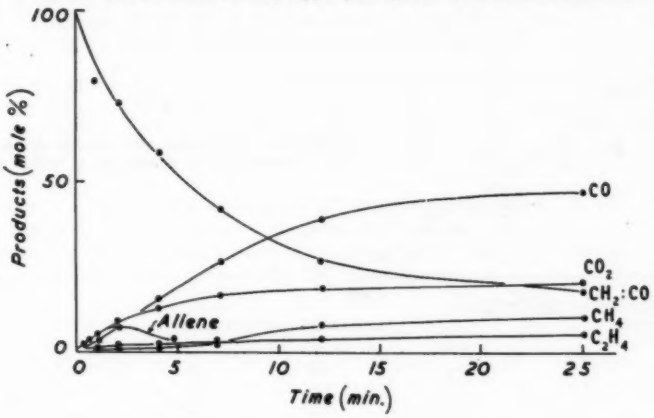
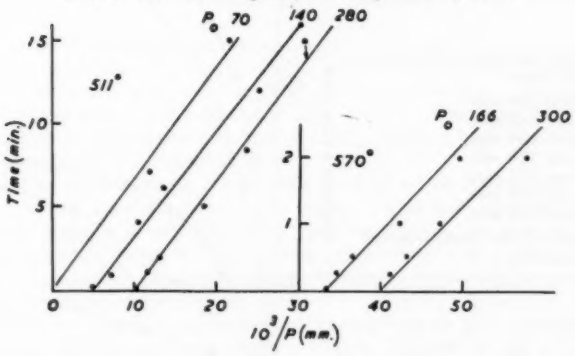


FIG. 3. *Second-order plots for decomposition of keten.*



and also for the experiments at 570°. The second-order rate constants so obtained have been used throughout for characterising the reaction and the results are given in Table 2.

TABLE 2. *Second-order velocity constants (mole^{-1} l. sec.$^{-1}$) for thermal decomposition of keten.*

	P_0 (mm.)						P_0 (mm.)		
Temp.	70	105	140	280	Mean k_c	Temp.	140	280	Mean k_c
511°	1·08	—	1·24	1·24	1·19	550°	3·13	—	3·13
522	—	1·72	1·70	—	1·71	554	—	3·64	3·64
535	2·28	—	2·07	—	2·17	570	6·0	6·9	6·4

The mean values for k_c give the Arrhenius plot shown in Fig. 4, from which the mean apparent activation energy is evaluated as 35·8 kcal. mole^{-1} and the rate constants are given by:

$$\ln k_c \text{ (mole}^{-1} \text{ l. sec.}^{-1}) = 23{\cdot}13 - 35{\cdot}8/RT$$

XUM

However, the plot is not perfectly linear and there is a suggestion that the activation energy is increasing throughout the temperature range studied; thus the three upper temperature points indicate E_a *ca.* 50 kcal. mole^{-1}.

Pressure–Time Curves and Material Balances.—Typical examples of the pressure–time curves are shown in Fig. 5. The ratio of the final to the initial pressure is approximately 1·15 in the temperature range 560—570° for initial pressures of about 200 mm. There is some indication that it may rise towards 1·25 at 600°. The exact variation was not investigated

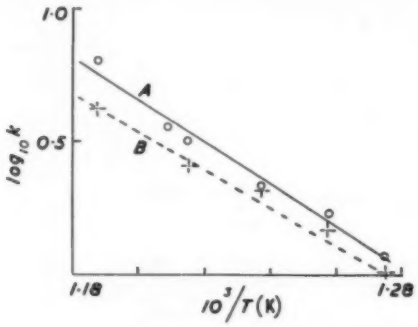


FIG. 4. *Arrhenius plots for (A) decomposition of keten and (B) formation of carbon dioxide.*

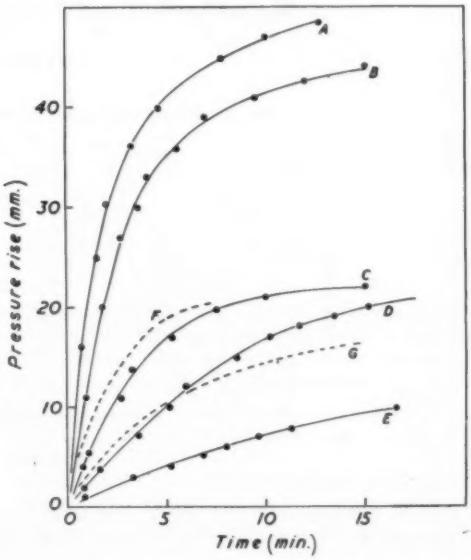


FIG. 5. *Rise in pressure during pyrolysis of keten.*

A, 568° *and* 300 *mm.*
B, 552° *and* 284 *mm.*
C, 552° *and* 150 *mm.*
D, 525° *and* 218 *mm.*
E, 510° *and* 135 *mm.*
F, 552° *and* 140 *mm.*
G, 510° *and* 135 *mm.*

For the significance of the broken curves see text.

since the slow breakdown of tars that accumulated in the neck of the bulb tended to produce slightly variable values under fixed conditions.

In early experiments, an initial pressure drop was observed. This fall could be as much as 4% of the initial pressure and diminished with successive runs, as reported by other workers.[1,2] The behaviour was consistent with the presence of a volatile polymerisable impurity which decreased in concentration as successive samples were removed from a sample stock. In support of this explanation it was found that the effect could be produced by deliberate addition of acetylene to the keten storage bulb. If successive samples were allowed to evaporate from the liquid mixture the pressure drop gradually diminished. As has already been mentioned, acetylene occurs in keten prepared by a keten lamp, and this material is concentrated in the keten fraction as purification proceeds.

XUM

Williamson [1] attributed the pressure drop to initial dimerisation of keten. Against this we have never observed its occurrence with keten of established purity. Moreover, we have performed several flow pyrolyses of keten without detecting its dimer in the products although the contact times were chosen to fall within the early diminished pressure region. This is in agreement with the observations by Rice and Roberts [8] that diketen is completely and quantitatively dissociated at ~500° in contact times of 0·04 sec.

An anomaly concerning the pressure–time curves is that the observed pressure at a given reaction time is always greater than the pressure calculated from the product analysis for that time. This is illustrated by the following comparison, giving the numbers of molecules in the system as determined by the two procedures for reaction at 550°:

	Reaction temp.	Initial pressure	Reaction time (min.) and no. of moles in system						
			0	¼	½	1	2	3½	5
From pressure ...	552°	284	100	101	102	104	105	111	112
By analysis	550°	280	100	97·0	95·4	93·1	95·0	96·4	98·9
Decomposition (%)			0	15	28	50	71	80	87

The discrepancy arises because compounds of high molecular weight are formed along with the products reported. An " average " formula for the material unaccounted for may be obtained by equating the molecular deficit to the deficit in the material balance. Thus for the case above we obtain the following results for 550° and 280 mm.:

Decomp.	Element recovery (% on keten decompd.)			Mols.	Average formula as lost material	
(%)	C	H	O	lost	C_x	H_y
15	59	60	101	4·0	3·1	3·0
28	64	69	92	6·6	3·1	2·6
50	57	49	100	10·9	4·0	4·7
71	55	45	100	10·0	6·4	7·8
80	50	39	98	14·6	5·5	6·7
87	52	40	99	13·1	6·4	8·0

Remembering that these figures are approximate, and combining all experimental errors additively, we may generalise the results and conclude: (i) oxygen recovery is complete; (ii) carbon recovery decreases from 60% to 50% during the reaction; (iii) hydrogen recovery decreases from 60% to 40% during the reaction; (iv) the " average " composition of the unanalysed products is substantially constant at C_nH_n, where n increases with reaction time. These features were evident at all temperatures.

The " average " formulæ indicate the kind of product which may occur. The chromatographic analyses revealed traces of acetylene in the early and increasing amounts of C_4 hydrocarbons in the late stages. In addition, tars and free carbon are formed. It is therefore evident that the unanalysed products have a wide range of molecular weight and probably of constitution also. The carbon : hydrogen ratios in these compounds are probably less than unity owing to the formation of free carbon.

For these reasons the observed pressure–time curves tend to give incomplete information concerning the actual decomposition of keten. This is revealed in Fig. 5 where the broken curves show the amounts of keten decomposed (obtained by analysis). In drawing these curves the scales were adjusted so that the final pressure ($= 1{\cdot}17 \times P_0$) is equal to total decomposition.

Decomposition in the Presence of Added Gases.—In order to investigate certain aspects of the reaction mechanism various runs were made with mixtures of keten with hydrogen, carbon monoxide, carbon dioxide, and propene severally.

Keten–hydrogen mixtures. A mixture of equal parts of keten and hydrogen was heated at 535° and 280 mm. total pressure. The product analyses are compared in Table 3 with those for the reaction of pure keten at 140 mm. and the same temperature. The obvious effects of hydrogen are: (i) a slight increase in the rate of disappearance of keten; (ii) general enhancement of methane formation; and (iii) enhancement of carbon monoxide formation which is more marked in the first part of the reaction. The decreasing recovery of hydrogen is certain evidence that hydrogen is removed in some important reaction. High accuracy is not claimed for these values owing to the large quantity of hydrogen which had to be estimated.

[8] Rice and Roberts, *J. Amer. Chem. Soc.*, 1943, **65**, 1677.

XUM

Keten–carbon monoxide mixtures. Equal parts of keten and carbon monoxide were heated at 535° and 280 mm. total pressure. The analyses for the mixtures were comparable with those for the pure reactant and there is no effect attributable to carbon monoxide.

[Similar results were obtained with carbon dioxide (10%) and with propene (10%). In the case of propene correction had to be made for the slow simultaneous decomposition of this compound, which lowered the accuracy of analysis.]

TABLE 3. *Products from pyrolysis of* 1 : 1 *keten–hydrogen mixture at* 535° *and* 280 *mm.*

Reaction time (min.)	H_2 Recovery (%)	CO	CH_4	C_2H_4	C_2H_6	CO_2	Keten	
1	100	11·2	3·2	1·2	0·3	7·7	67	
	—	7·6	0·8	1·1	0·4	7·1	72	H_2 absent
2	100	24·2	7·6	3·0	0·1	9·9	49	
	—	16·0	2·2	2·0	0·3	11·7	61	H_2 absent
4	98	38·2	14·9	1·8	0·6	11·7	28	
	—	30·2	4·3	3·7	0·1	13·2	45	H_2 absent
7	92	44·5	20·1	3·4	1·4	11·9	16	
	—	39·2	7·5	6·0	0·3	14·8	29	H_2 absent
12	80	55·7	24·9	3·8	1·3	10·9	12	
	—	50·8	10·6	5·3	1·3	17·2	16	H_2 absent

A more delicate test of the effect of propene was carried out at 510°, in which the amounts of carbon monoxide alone were measured during the early stages of the reaction. The results in Table 4 reveal no marked effect although the propene concentration was raised to 33%.

TABLE 4. *Comparative carbon monoxide analyses for the pyrolysis of pure keten and* 2 : 1 *keten–propene mixture at* 510° *and* 140 *mm.*

Reaction time (min.)	¼	½	¾	1	1½	1½	
Moles of CO per 100 moles	0·4	1·1	1·7	2·1	3·5	4·3	C_2H_6 absent
	0·4	1·2	—	3·4	—	5·5	33% C_2H_6

The significance of these results will be discussed in the following section.

DISCUSSION

Since the material balances show no loss of oxygen, carbon monoxide and dioxide together account for all the keten decomposed at a given instant. On the other hand, when we have allowed for methane, ethane, ethylene, and propene, the losses of carbon and hydrogen are still so high (40—50%) that we know relatively little of the hydrocarbon products of the decomposition. In these circumstances the main course which the reaction takes has to be argued from the form of the carbon monoxide and dioxide production curves and the secondary products have to be used as supporting evidence.

The formation of carbon dioxide alone gives curves with slopes at zero time approximately proportional to P_0^2, as shown by the following table:

Temp.	P_0 (mm.) of keten	$[d(CO_2)/dt]_{t=0}$ (mm. $min.^{-1}$)	P_0^2 (relative)	Rate (relative)
511°	70	8·75	1	1
511	140	8·4	4	4·8
511	273	19·2	15	11
522	105	5·7	1	1
522	142	11·1	1·8	1·9
535	70	4·2	1	1
535	199	16	4·2	3·8
550	144	29	1	1
550	290	69	4	2·4
570	166	58	1	1
570	300	135	3·2	2·3

Additional evidence of second-order dependence is provided by the fact that the slopes of the carbon dioxide curves fall to half their initial value at about 30% decomposition.

Since the early portions of the allene curves closely follow those for carbon dioxide, there is a strong probability that both these substances are products of the same bimolecular reaction, *viz.*, equation 2 (p. 2910). We are here in agreement with Akeroyd though his evidence for this step was less direct.

The initial rates of carbon dioxide formation have been reduced to a common P_0 (70 mm.) at each temperature by assuming a second-order equation and finally taking the mean rate. The resulting relative rates are:

Temp.	511°	522°	535°	550°	541°
Relative $[d(CO_2)/dt]_{t=0}$	1	1·5	2·2	3·2	5·2

The Arrhenius plot (Fig. 4) of these values is reasonably linear and gives an apparent activation energy of 37 kcal. mole^{-1}. We therefore regard the experimental activation energy from keten disappearance as reflecting the change in rate of reaction (2).

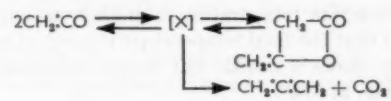
Photolysis studies of keten provide some support for reaction (2). Kistiakowsky and Marshall [9] demonstrated the presence of allene in low-temperature photolysis and conclusively proved that it did not result from reactions involving ethylene. At the same time they showed that the reactions (3) occurred:

$$\left.\begin{array}{l} :CH_2 + CO \longrightarrow CH_2{:}CO^* \\ CH_2{:}CO^* + M \longrightarrow CH_2{:}CO + M \end{array}\right\} \quad (3)$$

More recently Chanmugam and Burton,[10] investigating temperature effects on the photolysis, found that carbon dioxide, whose production was negligible at room temperature, became an increasingly important product at higher temperatures until at 412° their analysis was CO 53·07, CH_4 2·42, C_2H_4 16·06, C_2H_6 0·09, CO_2 13·45, C_2H_2 0·69, Tars 8·3%.

Whilst no connection between the formation of carbon dioxide and allene was suggested in either of the above papers, it seems consistent with the facts to suggest they are related by reaction (2), probably involving excited keten molecules at the lower temperatures.

The suggestion of reaction (2) together with the failure to observe diketen as a trace product does not exclude the possibility that diketen, or a transition complex based on it, occurs as an intermediate. Moreover, the accumulating evidence [11] in favour of the β-lactone structure of the dimer, helps to bring the present results into line with the pyrolyses of various β-lactones (to olefin and carbon dioxide) reported by Staudinger.[12] The objection to this scheme is the quantitative yield of keten observed by Rice and Roberts on pyrolysis of diketen. It would be possible by arbitrary adjustment of the relative magnitudes of the rate constants to explain all the observations in terms of the detailed mechanism for reaction (2) shown below:

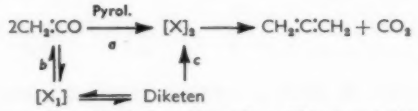


However, this scheme cannot be reconciled with the activation energies or the polarisation characteristics of the reactions involved. Thus the exothermic dimerisation proceeds slowly, if at all, in the gas phase at normal temperature, although a surface reaction occurs on the glass walls. This behaviour is paralleled in solution where the rate of dimerisation increases with polarity of the solvent and shows acid–base catalysis; for the uncatalysed reaction in acetone Rice and Greenburg [13] found an activation energy of 11 kcal. mole^{-1}.

[9] Kistiakowsky and Marshall, *J. Amer. Chem. Soc.*, 1952, **74**, 88.
[10] Chanmugam and Burton, *ibid.*, 1956, **78**, 509.
[11] Bader, Gutowsky, Williams, and Yankevick, *J. Amer. Chem. Soc.*, 1956, **78**, 2385.
[12] Staudinger, *Annalen*, 1907, **356**, 63; Staudinger and Kon, *ibid.*, 1911, **381**, 38.
[13] Rice and Greenburg, *J. Amer. Chem. Soc.*, 1934, **56**, 2132.

XUM

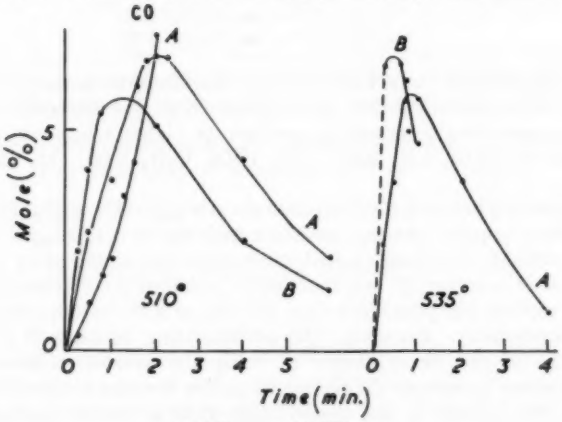
Thus the dimerisation probably involves a polarised transition state which can be reached in a suitable environment with a much lower activation energy than that required for reaction (2), namely, *ca.* 37 kcal. mole^{-1}. It is, therefore, suggested that the transition state involved in dimer-formation undergoes stabilising interactions with the solvent which distinguish it from that concerned in the pyrolysis. On the basis of this argument it is suggested that the relation of pyrolysis to dimerisation may be expressed by the following scheme:



a, $E_a \sim 37$; *b*, $E_a \sim 11$; *c*, $E_a \sim 37$ kcal. mole^{-1}.

The formation of carbon monoxide presents a more complex problem. There is a short induction period which, whilst scarcely discernible in the product trace of Fig. 2, appears in all other cases and has been confirmed by careful measurements at low conversions

FIG. 6. *Formation of allene and early formation of carbon monoxide.*



A, 140 *mm.* *B*, 280 *mm.*

(Fig. 6). The latter results have been reported in Table 4 where it is also shown that propene has no marked effect on the form of this induction. An explanation in terms of delayed attainment of the reaction temperature is unlikely as experiments with an inert gas (carbon dioxide) showed that the final temperature is reached in a few seconds. Moreover, formation of methane shows a similar but longer induction period, the maximum rate being reached in *ca.* 7 min. at 511°.

We wish first to decide whether the mechanism for carbon monoxide is independent of that for carbon dioxide formation, *i.e.*, whether we are dealing with simultaneous or consecutive reactions. Evidence against simultaneity can be deduced from consideration of CO_2 : CO ratios at various stages of decomposition. An estimate of the kinetic order of the carbon monoxide rate was obtained by ignoring the early induction period and drawing approximate tangents at zero time. This revealed that the initial rate is proportional to $P_0^{1.5}$, as shown by the following figures.

Temp.	511°	511°	511°	535°	535°	570°	570°
P_0 (mm.) of keten	70	140	280	70	140	166	300
$[d(CO)/dt]_{t=0}$ (mm. min.$^{-1}$)	3	6	25	4	12	75	135
Relative rate	1	2	8	1	3	1	2
Relative $P_0^{1.5}$	1	2·8	8·0	1	2·8	1	2·5

Let us assume for the moment that the exponent of P_0 is in fact unity; as will be seen, this leads to a simple result from which the effect of substituting other powers, including 3/2, can be deduced.

The detailed mechanism of carbon monoxide formation is irrelevant to our purpose provided it does not lead also to the formation of carbon dioxide. Since $d(CO + 2CO_2)/dt = -d(CH_2{:}CO)/dt$, straightforward integration of the rate equations for simultaneous first-order (carbon monoxide) and second-order (carbon dioxide) reactions gives the expressions:

$$P_{CO} = \frac{1}{\alpha} \ln \frac{A\alpha \exp(-k_1 t) - 1}{A\alpha - 1}$$

$$P_{CH_2:CO} = \frac{A \exp(-k_1 t)}{1 - A\alpha \exp(k_1 t)}$$

$$2P_{CO_2} = P_0 - (P_{CO} + P_{CH_2:CO})$$

where k_1 = first-order rate constant for CO formation, k_2 = second-order rate constant for CO_2 formation, $\alpha = k_2/k_1$ (mm.$^{-1}$), and $A = P_0/(1 + \alpha P_0)$ (mm.).

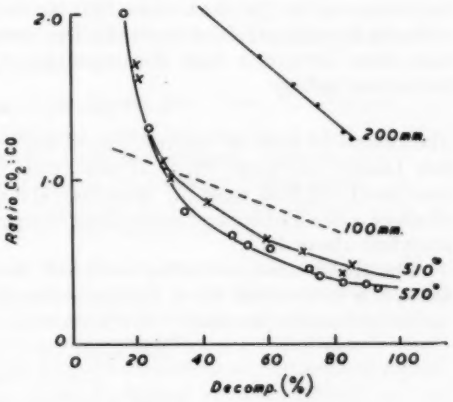


FIG. 7. CO_2 : CO *ratio as a function of decomposition.*

Curves: mixed initial pressures, × *at* 510° *and* ○ *at* 570°.

Straight lines: theoretical curves for $\alpha = 0{\cdot}025$ *and* $P_0 = 100$ (– – –) *and* 200 *mm.* (——).

Trial calculations showed that these equations gave curves broadly similar to the experimental ones for $0{\cdot}01 < \alpha < 0{\cdot}05$; by choosing $\alpha = 0{\cdot}025$, values of the CO_2 : CO ratio were obtained from the theoretical curves for various degrees of decomposition of keten.

In Fig. 7 we have plotted the calculated ratio curves for $P_0 = 100$ and 200 mm. and $\alpha = 0{\cdot}025$, together with the experimental ratio curves for 511° and 570°. It is apparent that there is a greater overall change in the experimental ratio than is shown by the theoretical plots. But even more striking is the effect of altering the initial pressure which, as might be expected, changes the theoretical curve but has no effect upon the experimental ratio.

We can reasonably infer what the effect of other choices of the order of simultaneous carbon monoxide formation on these curves would be. With formation of carbon monoxide also of the second order, *i.e.*, with the rates of formation of carbon monoxide and dioxide equally dependent on P_0, the CO_2 : CO ratio would be constant and independent of both the extent of decomposition and the pressure; as the assumed order of the carbon monoxide reaction decreased from two we would observe increasing dependence of the ratio on both initial pressure and on extent of reaction. It appears then that the experimental curves cannot be reconciled with a mechanism for carbon monoxide formation which is

XUM

independent of that for carbon dioxide formation and is of constant order with respect to keten over an appreciable range of decomposition.

Additional evidence against independence of these mechanisms can be deduced from the strikingly low temperature dependence of the CO_2 : CO ratio, as revealed in Fig. 7.

It follows, if the arguments are correct, that the mechanisms for formation of carbon dioxide and monoxide are linked in some way. Broadly, there are two possibilities to consider: (*a*) carbon dioxide is formed by reaction (2), and subsequent attack on keten by products derived from this reaction leads to the formation of carbon monoxide; and (*b*) carbon monoxide and dioxide both arise from long-lived activated keten molecules, which either decompose unimolecularly to carbon monoxide and a methylene radical, or react with another keten molecule to give carbon dioxide and allene.

The second proposal was originally made by Akeroyd; we would have to assume also, in order to explain the induction period now observed in carbon monoxide formation, that the methylene radicals initiate further breakdown of keten to carbon monoxide. It is, however, difficult to see how, on this basis, the CO_2 : CO ratio could be independent of P_0 since higher values of P_0 would still initially favour production of carbon dioxide at the expense of monoxide.

The first possibility is suggested both by the induction period in carbon monoxide formation and by the observation that the end of this induction period appears to coincide with the maximum in the curve of allene concentration. Accordingly one might suggest that allene initiates a chain decomposition of keten by splitting, to give acetylene and a methylene radical:

$$CH_2{:}C{:}CH_2 \longrightarrow C_2H_2 + {:}CH_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The calculated heat of this reaction, if one assumes that methylene is in its lowest state (see Laidler and Casey [14]), is 77 kcal. mole^{-1}, which is not very different from that for reaction (1) (71 kcal. mole^{-1}). Reaction (4) is not in conflict with the little known properties of allene, since Fichter and Spiegelberg [15] reported its breakdown to methane, ethane, and acetylene above 500°.

The continuation of carbon monoxide formation by attack of methylene radicals on keten is a speculation but a slightly expanding chain is required to maintain the rate of carbon monoxide formation. We tentatively suggest that the propagating stages may be:

$$\begin{aligned}
{:}CH_2 + CH_2{:}CO &\longrightarrow {\cdot}CH_3 + {\cdot}CH{:}CO \\
{\cdot}CH{:}CO &\longrightarrow {\vdots}CH + CO \\
{\cdot}CH_3 + CH_2{:}CO &\longrightarrow CH_4 + {\cdot}CH{:}CO \\
{\vdots}CH + CH_2{:}CO &\longrightarrow {:}CH_2 + {\cdot}CH{:}CO
\end{aligned}$$

Termination by combination of methylene radicals to ethylene could then be more important in the early stages (accounting for the initial rise in ethylene concentration), whilst later other processes involving the new radicals predominate. The high material loss (giving tars and higher hydrocarbons) exemplifies the complexity of the situation. The effects of hydrogen addition (*i.e.*, increasing rate and enhancing methane production) could result from modification of the propagation stages by reactions such as:

$$\begin{aligned}
H_2 + {\cdot}CH_3 &\longrightarrow CH_4 + H{\cdot} \\
H{\cdot} + CH_2{:}CO &\longrightarrow {\cdot}CH_3 + CO
\end{aligned}$$

The existence of such a mechanism is favoured by observations by Chanmugam and Burton [10] and Knox, Norrish, and Porter,[16] who found that the quantum yield of keten photolysis increased with temperature. It is also relevant that whilst the former workers found appreciable carbon dioxide and little acetylene at 412°, the latter achieved instantaneous temperatures of between 500° and 800° in high-intensity flash photolysis, finding no carbon dioxide but appreciable amounts of acetylene.

[14] Laidler and Casey, *J. Chem. Phys.*, 1949, **17**, 1087.
[15] Fichter and Spiegelberg, *Helv. Chim. Acta*, 1929, **12**, 1161.
[16] Knox, Norrish, and Porter, *J.*, 1952, 1477.

XUM

Thus there seems to be strong evidence that the chain mechanism of breakdown of keten never leads to carbon dioxide and is favoured by increasing temperature. On the arbitrary assumption that every allene molecule formed provides a methylene radical for chain propagation, and using the limiting CO_2 : CO ratios of 0·4 at 510° and 0·34 at 570°, we estimate the chain length to be 2·5 at 510° and 3·0 at 570°. These values compare with quantum yields of 2 at 412° [10] and 6 at 700—900°.[15] The comparison is reasonable even though our estimates are probably lower than the actual lengths of the chains. This temperature effect suggests that at least one of the propagation stages has a sensible activation energy but nothing more can be said on the basis of this tentative mechanism.

In future work it will be important to establish the nature of chain initiation and a decision between the two possibilities presented might be made by study of the decomposition of allene and its effect on the breakdown of keten supported by low-pressure pyrolyses of keten.

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BRITISH CELANESE LTD., RESEARCH LABORATORIES,
PUTTERIDGE BURY, nr. LUTON, BEDS. [*Received, February 4th*, 1958.]

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595 *The Preparation of Some Esters of Methyl* 4 : 6-O-*Benzylidene*-α-D-*altroside.**

By K. S. ENNOR, JOHN HONEYMAN, C. J. G. SHAW, and THEO. C. STENING.

Several nitrate and toluene-*p*-sulphonate esters of methyl 4 : 6-*O*-benzylidene-α-D-altroside have been prepared and characterized. Attention is drawn to the extreme sensitivity to alkali of the 2-toluene-*p*-sulphonate ester, which is converted into methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-alloside even on being chromatographed on acid-washed alumina.

NITRATION of methyl 4 : 6-*O*-benzylidene-α-D-altroside (I) with excess of fuming nitric acid in acetic anhydride gives the 2 : 3-dinitrate (III), but use of one molecular proportion of acid leads to the 3-mononitrate (II). This is similar to the unimolar nitrations of methyl 4 : 6-*O*-benzylidene-α-D-glucoside [1] and methyl 4 : 6-*O*-ethylidene-α-D-mannoside [2] which also give the corresponding 3-nitrates. Methyl 4 : 6-*O*-benzylidene-α-D-altroside 3-nitrate has been prepared by the action of sodium nitrite in boiling aqueous ethanol on the corresponding 2 : 3-dinitrate. Again this is similar to the 2 : 3-dinitrates of methyl 4 : 6-*O*-benzylidene-α-D-glucoside [3] and methyl 4 : 6-*O*-ethylidene-α-D-mannoside [4] which preferentially lose the nitrate group from $C_{(2)}$. The 3-nitrate (II) has been characterized by nitration to the 2 : 3-dinitrate and conversion, through methylation, denitration, and toluene-*p*-sulphonylation, into known methyl 4 : 6-*O*-benzylidene-2-*O*-methyl-α-D-altroside 3-toluene-*p*-sulphonate [5] (IV).

Two methods have been employed for reducing nitrates of methyl 4 : 6-*O*-benzylidene-α-D-altroside. Hydrazine hydrate converts both the 2 : 3-dinitrate (III) and the 3-nitrate (II) into the parent alcohol (I) in good yield, but the 3-nitrate 2-toluene-*p*-sulphonate (V) gives a mixture of methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-alloside (VII) (24%) and methyl 4 : 6-*O*-benzylidene-α-D-altroside 2-toluene-*p*-sulphonate (VI) (66%). The latter is very sensitive to alkaline media and is wholly or partly converted into the anhydro-compound (VII) merely on being chromatographed on ordinary or acid-washed alumina.

* An abstract of this paper was presented at the New York meeting of the American Chemical Society, September, 1957.

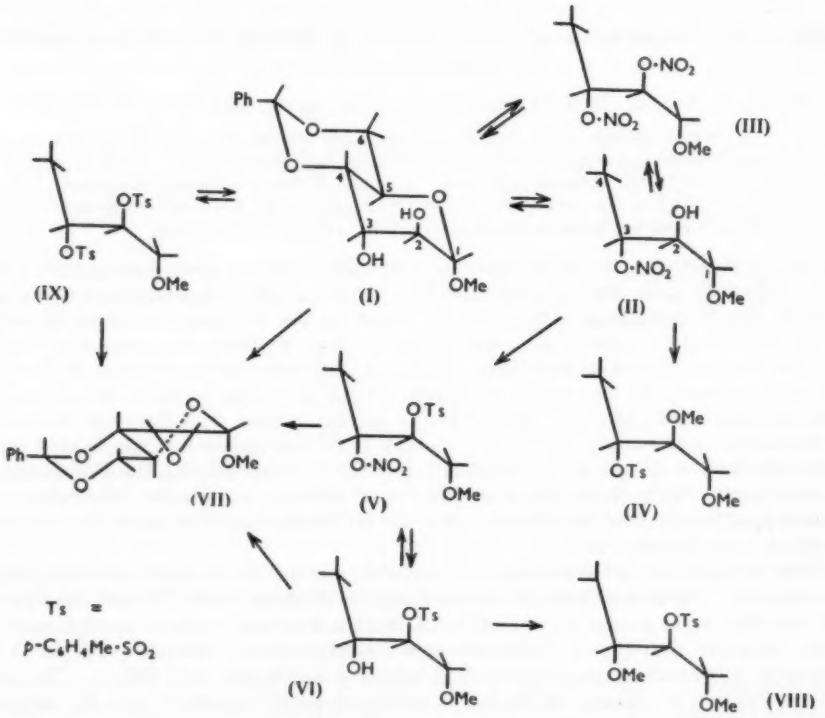
[1] Honeyman and Stening, *J.*, 1958, 537.
[2] Aspinall and Zweifel, *J.*, 1957, 2271.
[3] Honeyman and Morgan, *J.*, 1955, 3660.
[4] Honeyman and Stening, *J.*, 1957, 2278.
[5] Robertson and Griffith, *J.*, 1935, 1193.

XUM

Although hydrazine is only a weak base, the reaction medium is sufficiently alkaline to bring about elimination of the toluene-*p*-sulphonate group with inversion of the configuration at $C_{(2)}$. The diaxial system of 2-toluene-*p*-sulphonyloxy- and 3-hydroxyl groups gives a planar system which is most favourable for a base-catalysed intramolecular S_N2 reaction leading to the 2 : 3-α-D-*allo*-epoxide.[6] In marked contrast to the 2-toluene-*p*-sulphonate, the 2 : 3-ditoluene-*p*-sulphonate of methyl 4 : 6-*O*-benzylidene-α-D-altroside is unaffected by hydrazine hydrate and is much more stable to alkali: it can, for example, be chromatographed on ordinary alumina without change.

In the second method catalytic hydrogenation of methyl 4 : 6-*O*-benzylidene-α-D-altroside 3-nitrate 2-toluene-*p*-sulphonate at room temperature under pressure, with palladium–charcoal, gives an almost quantitative yield of methyl 4 : 6-*O*-benzylidene-α-D-altroside 2-toluene-*p*-sulphonate. Under these neutral conditions, conversion of the 2-toluene-*p*-sulphonate into the 2 : 3-*allo*-epoxide is prevented. The amorphous product was characterized by nitration to the 3-nitrate 2-toluene-*p*-sulphonate and by methylation to the 3-*O*-methyl 2-toluene-*p*-sulphonate [7] (VIII).

Attempts to prepare methyl 4 : 6-*O*-benzylidene-α-D-altroside 2-toluene-*p*-sulphonate by selective sulphonylation of methyl 4 : 6-*O*-benzylidene-α-D-altroside all failed. When



one mole of toluene-*p*-sulphonyl chloride is used at 0° for 16 hr., only the 2 : 3-ditoluene-*p*-sulphonate (IX) and unchanged compound (I) were isolated. Similar experiments at −15° with a shorter reaction time gave methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-alloside (VII) in addition to (IX) and (I). It appears probable that any

[6] Newth, *J.*, 1956, 441.
[7] Gut and Prins, *Helv. Chim. Acta*, 1946, **29**, 1555.

2-toluene-*p*-sulphonate ester formed during these sulphonylation experiments is converted into methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-alloside on the alumina column.

Experimental

Unless otherwise stated, specific rotations were determined for $CHCl_3$ solutions, the light petroleum used had b. p. 60—80°, solutions in chloroform or benzene were dried over sodium sulphate, and solvents were evaporated at reduced pressure.

" Alumina " refers to activated alumina, Type H, 100/200 S mesh, supplied by Messrs. Peter Spence & Sons, Ltd. Acid-washed alumina, " WOELM," is supplied by Messrs. L. Light & Co., Ltd. Hydrazine hydrate was 100% B.D.H. Laboratory Reagent.

Where appropriate, mixed m. p. were determined to help to establish identities.

Methyl 4 : 6-O-*Benzylidene*-α-D-*altroside* 2 : 3-*Dinitrate*.—An ice-cold solution of fuming nitric acid (*d* 1·5; 4 ml., 0·09 mole) in acetic anhydride (10 ml.) was added slowly to a suspension of methyl 4 : 6-*O*-benzylidene-α-D-altroside (5 g., 0·018 mole) in acetic anhydride (10 ml.) at 0°. After 20 min. at room temperature, the mixture was poured into ice-water containing potassium carbonate. The crude syrup was chromatographed in benzene solution on alumina, and the syrup obtained by elution with benzene was dissolved in warm methanol and reprecipitated in ice-water. After several weeks the syrup solidified to give *methyl* 4 : 6-O-*benzylidene*-α-D-*altroside* 2 : 3-*dinitrate* (70%), m. p. 48—49° (Found: C, 45·6; H, 4·5; N, 7·3. $C_{14}H_{16}O_{10}N_2$ requires C, 45·2; H, 4·3; N, 7·5%).

Similar preparations were carried out with different reaction times, but the syrups solidified with difficulty only after long storage under water.

Methyl 4 : 6-O-*Benzylidene*-α-D-*altroside* 3-*Nitrate*.—(*a*) A solution of the 2 : 3-dinitrate (4·5 g.) in 80% aqueous ethanol (50 ml.) containing sodium nitrite (2·5 g.) was boiled under reflux for 16 hr. Evaporation left a white solid which was extracted twice with chloroform. On evaporation, the chloroform extracts yielded a solid which, recrystallized from light petroleum–ethanol, was *methyl* 4 : 6-O-*benzylidene*-α-D-*altroside* 3-*nitrate* (2·18 g., 55%), m. p. 156—157°, $[\alpha]_D^{19}$ +118° (Found: C, 51·6; H, 5·4; N, 4·3. $C_{14}H_{17}O_8N$ requires C, 51·4; H, 5·2; N, 4·3%).

(*b*) Fuming nitric acid (*d* 1·5; 0·85 ml., 0·019 mole) in acetic anhydride (5 ml.) was dropped into an ice-cold solution of methyl 4 : 6-*O*-benzylidene-α-D-altroside (4·2 g., 0·015 mole) in chloroform (20 ml.) and acetic anhydride (10 ml.). After 1 hr., the mixture was shaken with dilute potassium carbonate solution. The chloroform layer was washed twice with water before being evaporated. The resulting syrup was dissolved in benzene and chromatographed on alumina. Elution with benzene yielded a syrup (0·5 g.) which has not crystallized. The chloroform eluant gave a white solid which, recrystallized from ethanol–light petroleum, was the 3-nitrate (25%), m. p. 156—157°.

(*c*) Fuming nitric acid (*d* 1·5; 8 ml.) in acetic anhydride (20 ml.) was added slowly to methyl 4 : 6-*O*-benzylidene-α-D-altroside (10 g.) suspended in acetic anhydride (20 ml.) at 0°. After 10 min. at room temperature, the resulting solution was poured into ice-water containing potassium carbonate. The precipitated syrup was separated and the aqueous solution was extracted twice with chloroform. The combined product and the chloroform solutions were washed with aqueous potassium carbonate, then with water. Evaporation of the chloroform yielded a syrup (11·7 g.) which was boiled under reflux for 16 hr. with sodium nitrite (6·4 g.) in 80% ethanol (130 ml.). The solution was evaporated and the residue was extracted with chloroform. Evaporation left a solid which, recrystallized from ethanol–light petroleum, was the 3-nitrate (30%), m. p. 155—156°.

Characterization of Methyl 4 : 6-O-*Benzylidene*-α-D-*altroside* 3-*Nitrate*.—(*a*) Silver oxide (1·5 g.) was added during 5 hr. to methyl 4 : 6-*O*-benzylidene-α-D-altroside 3-nitrate (0·47 g.) suspended in boiling methyl iodide (10 ml.). Boiling was continued for a further 19 hr., then the mixture was cooled, filtered, and evaporated to a syrup which was extracted several times with chloroform. The evaporated extracts although purified by chromatography on alumina in benzene did not yield a crystalline product. A solution of the product and sodium sulphide (0·8 g.) in ethanol (50 ml.) was left at room temperature for 24 hr. The solution was filtered, and water was added to the filtrate, which was then concentrated. The residue was extracted with chloroform. Evaporation of the chloroform yielded a syrup, which was dissolved in pyridine (5 ml.), and to this was added a solution of toluene-*p*-sulphonyl chloride (0·5 g.) in pyridine (5 ml.) at 0°. After 4 days at 0°, the solution was poured into ice-water, and the

XUM

solidified product, recrystallized from methanol, was methyl 4 : 6-*O*-benzylidene-2-*O*-methyl-α-D-altroside 3-toluene-*p*-sulphonate (0·31 g.), m. p. 165—166°.

(*b*) Fuming nitric acid (*d* 1·5; 0·3 ml.) in acetic anhydride (1 ml.) was added slowly at 0° to a suspension of the 3-nitrate (0·3 g.) in acetic anhydride (2 ml.). After 15 min. at 0°, the mixture was poured into ice-water. The resulting syrup solidified, to afford 4 : 6-*O*-benzylidene-α-D-altroside 2 : 3-dinitrate (0·3 g., 88%), m. p. 48—49°.

Reduction of Methyl 4 : 6-O-*Benzylidene-α-D-altroside* 2 : 3-*Dinitrate and* 3-*Nitrate with Hydrazine.*—A solution of methyl 4 : 6-*O*-benzylidene-α-D-altroside 2 : 3-dinitrate (1·49 g., 0·004 mole) and hydrazine hydrate (1·20 g., 0·024 mole) in ethanol (15 ml.) was boiled under reflux for 90 min. After excess of hydrazine had been decomposed by boiling the solution with Raney nickel, the solution was filtered and evaporated. The solid residue, recrystallized from methanol, was methyl 4 : 6-*O*-benzylidene-α-D-altroside (74%), m. p. 170°, $[\alpha]_D^{18}$ +116° (*c* 0·6).

The above method when applied to the 3-nitrate gave a solution, which after evaporation yielded methyl 4 : 6-*O*-benzylidene-α-D-altroside (98%), m. p. 169—170°.

*Preparation of the Methanesulphonate and Toluene-*p*-sulphonate of Methyl* 4 : 6-O-*Benzylidene-α-D-altroside* 3-*Nitrate.*—A solution of the 3-nitrate (0·85 g.) and methanesulphonyl chloride (0·37 g.) in pyridine (2·5 ml.) was left at room temperature for 3 days, then poured into ice-water, and the resulting solid (1·0 g.) was washed with water, dried, and recrystallized from methanol to give needles of *methyl* 4 : 6-O-*benzylidene-α-D-altroside* 2-*methanesulphonate* 3-*nitrate* (0·87 g., 83%), m. p. 157—158°, $[\alpha]_D^{21}$ +52·6° (*c* 2·5) (Found: C, 44·6; H, 4·7; S, 8·1. $C_{15}H_{19}O_{10}NS$ requires C, 44·4; H, 4·7; S, 7·9%).

Similar treatment of the 3-nitrate (0·95 g.) and toluene-*p*-sulphonyl chloride (0·95 g.) in pyridine (4 ml.) at room temperature for 4 days gave *methyl* 4 : 6-O-*benzylidene-α-D-altroside* 3-*nitrate* 2-*toluene*-p-*sulphonate* (1·1 g., 79%), m. p. 147°, $[\alpha]_D^{19}$ +39·6° (*c* 1·3) (Found: C, 52·2; H, 5·0. $C_{21}H_{22}O_{10}NS$ requires C, 52·4; H, 4·8%).

Preparation and Characterization of Methyl 4 : 6-O-*Benzylidene-α-D-altroside* 2-*Toluene*-p-*sulphonate.*—Reduction of the 3-nitrate 2-toluene-*p*-sulphonate (1·20 g., 0·0025 mole) with hydrazine hydrate (0·37 g., 0·0075 mole) in ethanol (12 ml.) was carried out as described for the 2 : 3-dinitrate. The cooled, filtered reaction solution deposited needles which, recrystallized from ethanol, were methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-alloside (0·10 g., 15%), m. p. 196—197°, $[\alpha]_D^{18}$ +141° (*c* 0·8). The remaining reaction solution was evaporated to a syrup which was chromatographed in benzene on acid-washed alumina. After benzene had failed as eluant, elution with benzene–chloroform yielded, in the early fractions, the anhydro-α-D-alloside (0·06 g., 9%), m. p. 196—197°. Further elution with benzene–chloroform gave *methyl* 4 : 6-O-*benzylidene-α-D-altroside* 2-*toluene*-p-*sulphonate* (0·72 g., 66%), an amorphous solid even after repeated separation from ethanol, $[\alpha]_D^{20}$ +44·5° (*c* 3·0) (Found: C, 57·4; H, 5·6; S, 7·1. $C_{21}H_{24}O_8S$ requires C, 57·8; H, 5·5; S, 7·3%).

A solution of the 3-nitrate 2-toluene-*p*-sulphonate (2·50 g.) in methanol (150 ml.) was shaken with palladium–charcoal (2·5 g.) under hydrogen (20 atm.) at room temperature during 30 min. The catalyst was filtered off and washed with warm methanol, and the combined filtrate and washings were evaporated to give the amorphous 2-toluene-*p*-sulphonate (2·20 g., 97%).

Fuming nitric acid (*d* 1·5; 0·06 ml.) in acetic anhydride (0·2 ml.) was added slowly to a solution of the 2-toluene-*p*-sulphonate (0·40 g.) in acetic anhydride (0·3 ml.) at 0°. After 10 min. at room temperature, the solution was poured into ice-water containing potassium carbonate. The resulting solid, recrystallized from methanol, was methyl 4 : 6-*O*-benzylidene-α-D-altroside 3-nitrate 2-toluene-*p*-sulphonate (0·29 g., 66%), m. p. 144—145°, $[\alpha]_D^{25}$ +39·7° (*c* 1·2).

Silver oxide (1 g.) was added in portions to a suspension of the 2-toluene-*p*-sulphonate (0·50 g.) in boiling methyl iodide (3 ml.) during 2 hr. The mixture was boiled for 4 hr. more before the silver residue was filtered off and washed with acetone, and the combined filtrate and washings were evaporated to a solid. This was chromatographed in benzene on acid-washed alumina. Elution with benzene yielded a solid which, recrystallized from methanol, was methyl 4 : 6-*O*-benzylidene-3-*O*-methyl-α-D-altroside 2-toluene-*p*-sulphonate (0·38 g., 74%), m. p. 140—141°, $[\alpha]_D^{23}$ +53·0° (*c* 1·4) (Found: C, 58·7; H, 5·9. Calc. for $C_{22}H_{26}O_8S$: C, 58·7; H, 5·8%).

Effect of Alumina on Methyl 4 : 6-O-*Benzylidene-α-D-altroside* 2-*Toluene*-p-*sulphonate.*—The 2-toluene-*p*-sulphonate (0·20 g.) was chromatographed on alumina in benzene. Washing

XUM

the column with benzene yielded methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-alloside (0·12 g., 99%), m. p. 200—201°, $[\alpha]_D^{23}$ +139° (*c* 0·6).

The 2-toluene-*p*-sulphonate (0·052 g.) was chromatographed in benzene (10 ml.) on acid-washed alumina. Elution with benzene–chloroform removed methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-alloside (90%), m. p. 195—196° (from methanol–chloroform).

Reaction of Methyl 4 : 6-O-*Benzylidene*-α-D-*altroside* 2 : 3-*Ditoluene*-p-*sulphonate with Sodium Iodide in Acetone and with Hydrazine.*—(*a*) A sealed tube containing the 2 : 3-ditoluene-*p*-sulphonate (1·18 g., 0·002 mole) and sodium iodide (0·90 g., 0·006 mole) dissolved in acetone (20 ml.) was heated at 100° for 46 hr. The colourless solution was evaporated and the residue was extracted with chloroform which, on evaporation, yielded unchanged starting compound (1·15 g., 97%), m. p. 178°, $[\alpha]_D^{20}$ +46·0° (*c* 2·1).

(*b*) A solution of the 2 : 3-ditoluene-*p*-sulphonate (1·18 g., 0·002 mole) and hydrazine hydrate (0·6 g., 0·012 mole) in ethanol (5 ml.) and chloroform (5 ml.) was boiled under reflux for 1·5 hr. The solution was boiled with Raney nickel for 15 min., filtered, and evaporated. The residual solid, recrystallized from ethanol–acetone, was unchanged starting compound (1·06 g., 90%), m. p. 178°, $[\alpha]_D^{20}$ +46·6° (*c* 1·3).

Attempted Selective Sulphonylation of Methyl 4 : 6-O-*Benzylidene*-α-D-*altroside.*—(*a*) This altroside (5·0 g., 0·018 mole) was dissolved in pyridine (14 ml.) and cooled to 0°. A cold solution of toluene-*p*-sulphonyl chloride (3·8 g., 0·020 mole) in pyridine (14 ml.) was added slowly, and the mixture kept at room temperature for 16 hr. Water (1 ml.) was added, and after 2 hr. the mixture was diluted with water and extracted with chloroform. The chloroform extract was washed successively with 2N-hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water, then evaporated to a yellow syrup. On the addition of ether and light petroleum, a white solid was formed which, recrystallized from methanol–chloroform, was methyl 4 : 6-*O*-benzylidene-α-D-altroside 2 : 3-ditoluene-*p*-sulphonate (1·9 g., 18%), m. p. 176—178°, $[\alpha]_D^{21}$ +45·0° (*c* 1·0). The remaining syrup (4·1 g.) was chromatographed in benzene on alumina. Elution with benzene and benzene–ether gave a white solid (1·6 g.), which recrystallized from methanol–chloroform was also 2 : 3-ditoluene-*p*-sulphonate (15%). Elution with chloroform and methanol gave white crystals which, recrystallized from methanol–chloroform, were unchanged methyl 4 : 6-*O*-benzylidene-α-D-altroside (1·3 g., 26%), m. p. 169—170°, $[\alpha]_D^{20}$ +121° (*c* 1·0).

(*b*) The above esterification was repeated at −15° for 6 hr. The resulting syrup, which did not yield crystals on addition of ether, was chromatographed in benzene on alumina. Elution with benzene gave methyl 4 : 6-*O*-benzylidene-α-D-altroside 2 : 3-ditoluene-*p*-sulphonate (0·15 g., 2%). Elution with benzene–ether (9 : 1) gave a white solid (0·85 g., 17%) which, recrystallized from methanol–chloroform, was methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-alloside, m. p. 195—196°, $[\alpha]_D^{21}$ +138° (*c* 1·9). Successive elutions with benzene–ether, ether, and ether–chloroform gave small amounts of unidentified syrups (0·35 g.). Elution with chloroform, chloroform–methanol (2 : 1), and methanol gave a white solid (1·53 g., 36%), which, recrystallized from methanol–ether, was unchanged methyl 4 : 6-*O*-benzylidene-α-D-altroside, m. p. 169—171°.

(*c*) A third experiment was carried out at −16° for 4 hr. The mixture was examined as above except that the chromatography was done on acid-washed alumina. No product was eluted with benzene or benzene–ether (9 : 1). Benzene–ether (1 : 1), ether, and ether–chloroform (9 : 1) removed methyl 4 : 6-*O*-benzylidene-α-D-altroside 2 : 3-ditoluene-*p*-sulphonate (1·1 g., 13%). Elution with ether–chloroform (1 : 1, and 1 : 4) gave methyl 2 : 3-anhydro-4 : 6-*O*-benzylidene-α-D-alloside (0·6 g., 16%). Chloroform–methanol (2 : 1) and methanol gave unchanged starting compound (0·9 g., 14%).

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UNIVERSITY OF LONDON, KING'S COLLEGE,
STRAND, LONDON, W.C.2.

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XUM

596. *The Fries Rearrangement. Part V.* Effect of the Ring Substituent and the Acyl Group.*

By N. M. Cullinane and B. F. R. Edwards.

Rearrangements of phenyl, *o*-, *m*-, and *p*-tolyl acetate and benzoate were examined at high temperature in the absence of solvent, and at low temperature in solution. With the phenyl and *o*- and *m*-tolyl esters both *ortho*- and *para*-substitution took place, the benzoates giving a higher *para* : *ortho* ratio than the acetates. The *p*-tolyl esters underwent an *ortho*-shift only, and in the reactions in solution titanic chloride was a more active catalyst than aluminium chloride. Reactions in nitrobenzene were faster and gave a higher proportion of *p*-hydroxy-ketones than did the corresponding reactions in ethylene dichloride.

Phenyl acetate, propionate, *n*-butyrate, *iso*butyrate, and octanoate yielded mainly *para*-substituted products, the proportion of the *ortho*-isomer increasing with the size of the acyl group and with the branching of the chain.

The position of an alkyl group substituted in the ring has a considerable influence on the proportion of *o*- and *p*-hydroxy-ketones formed in the Fries rearrangement of phenol esters. The results of earlier work,[1] carried out mainly with aluminium chloride as catalyst, are not readily comparable since the experimental conditions varied widely, but it has been found in general that *o*-tolyl esters yield predominantly *p*-, and *m*-tolyl esters *o*-hydroxy-ketones, while *p*-tolyl esters give exclusively *o*-hydroxy-ketones.

In the present work phenyl, *o*-, *m*-, and *p*-tolyl acetate and benzoate were treated with aluminium chloride and titanic chloride (*a*) at high temperature in the absence of solvent and (*b*) at low temperature in homogeneous solution. In the high-temperature experiments considerable decomposition occurred with titanic chloride, especially in the transformation of acetates, and with both sets of esters this catalyst was less active than aluminium chloride. In general, the isomerisation of benzoates was the slower reaction and also less *ortho*-shift took place. Production of varying amounts of the phenol was observed in all the reactions studied. The products of the low-temperature experiments, where nitrobenzene and ethylene dichloride were the solvents, were determined quantitatively; it was found that more *ortho*-substituted ketone was obtained in the titanic chloride-catalysed migrations.

The phenyl esters gave both *o*- and *p*-hydroxy-ketones, chiefly the latter, especially in the benzoate rearrangements. *o*-Tolyl acetate underwent chiefly a *para*-shift, although at the higher temperature the proportion of the *ortho*-product increased; no *ortho*-migration occurred with the benzoate. *m*-Tolyl acetate and benzoate yielded predominantly the *ortho*-isomers at high temperature. In the low-temperature reactions mainly *para*-substitution was observed in the benzoate transformation with both catalysts; the acetate afforded mainly the *ortho*-product with the titanic and the *para*-product with the aluminium halide under these conditions. Only *ortho*-shifts occurred in the transformation of the *p*-tolyl esters; for the reactions in solution titanic chloride was found to be the more active agent.

For the rearrangement of phenyl octanoate Ralston, McCorkle, and Bauer [2] observed a higher *para* : *ortho*-ratio of hydroxy-ketones in nitrobenzene than in *s*-tetrachloroethane. We found that the solvent had a marked effect on this ratio, as well as on the rate of reaction. Thus in the aluminium chloride-catalysed reactions *m*-tolyl acetate, dissolved in the more

* Part IV, *J.*, 1958, 434.

[1] Cf. Blatt, *Org. Reactions*, 1942, **1**, p. 342.
[2] Ralston, McCorkle, and Bauer, *J. Org. Chem.*, 1940, **5**, 645.

XUM

polar nitrobenzene, underwent in the main *para*-substitution, but use of ethylene dichloride led mainly to *ortho*-substitution, the reaction being slower in the latter medium. Titanic chloride induced *ortho*-substitution mainly in nitrobenzene and a still greater *ortho*-shift in ethylene dichloride. In general, aluminium chloride was a more powerful catalyst than titanic chloride, and caused a greater amount of *para*-migration.

Rearrangement of acetates.

		(a) *In the absence of solvent.*				(b) *In nitrobenzene solution.*				
		Phenol	Hydroxy-ketones			Phenol	Hydroxy-ketones			Ester recovd.
	Catalyst	(%)	*o* (%)	*p* (%)	*o*/*p*	(%)	*o* (%)	*p* (%)	*o*/*p*	(%)
Phenyl	$AlCl_3$	0·0	46·4	41·7	1·2	11·6	11·4	72·8	0·16	0·0
	$TiCl_4$	29·3	19·7	14·9	1·3	18·3	11·3	65·6	0·17	0·0
o-Tolyl	$AlCl_3$	0·0	24·1	61·3	0·4	0·0	4·1	81·8	0·05	0·0
	$TiCl_4$	20·0	9·7	12·1	0·8	0·0	7·3	74·5	0·10	0·0
m-Tolyl	$AlCl_3$	0·0	89·0	6·5	14·0	4·0	43·9	46·0	1·0	0·0
	$TiCl_4$	16·1	34·3	1·0	34·0	4·6	72·5	13·9	5·2	0·0
p-Tolyl	$AlCl_3$	6·4	91·5	—	—	12·6	74·0	—	—	12·1
	$TiCl_4$	27·8	61·4	—	—	4·0	84·4	—	—	0·9

Rearrangement of benzoates.

(c) *In the absence of solvent.*

			Hydroxy-ketones				
Benzoate	Catalyst	Phenol (%)	*o* (%)	*p* (%)	*o*/*p*	Ester recovd. (%)	Benzoic acid (%)
Phenyl	$AlCl_3$	0·0	27·4	69·6	0·4	0·0	0·0
	$TiCl_4$	11·4	23·1	58·0	0·4	0·0	10·8
o-Tolyl	$AlCl_3$	3·0	0·0	86·3	—	0·0	2·5
	$TiCl_4$	11·8	0·0	69·2	—	0·0	11·6
m-Tolyl	$AlCl_3$	0·0	89·0	3·0	30·0	0·0	0·0
	$TiCl_4$	10·1	82·3	0·0	—	0·0	9·7
p-Tolyl	$AlCl_3$	4·6	88·1	—	—	0·0	4·0
	$TiCl_4$	1·4	78·0	—	—	0·0	0·0

(d) *In nitrobenzene solution.*

Phenyl	$AlCl_3$	5·1	8·9	80·5	0·11	0·0	4·9
	$TiCl_4$	3·9	7·4	83·7	0·09	0·0	4·0
o-Tolyl	$AlCl_3$	6·2	0·0	91·1	—	0·0	6·0
	$TiCl_4$	5·5	0·0	89·0	—	0·0	5·2
m-Tolyl	$AlCl_3$	6·9	14·9	67·7	0·22	0·0	6·6
	$TiCl_4$	19·6	27·0	48·0	0·56	0·0	19·1
p-Tolyl	$AlCl_3$	12·7	38·0	—	—	32·0	12·3
	$TiCl_4$	9·2	57·2	—	—	14·8	8·9

Rearrangement of m-*tolyl acetate.*

			Hydroxy-ketones			
Solvent	Catalyst	*m*-Cresol (%)	*o* (%)	*p* (%)	*o*/*p*	Ester recovd. (%)
Nitrobenzene	$AlCl_3$	1·5	27·7	66·1	0·4	0·0
Ethylene dichloride	$AlCl_3$	4·1	42·1	24·9	1·7	9·8
Nitrobenzene	$TiCl_4$	12·7	55·1	20·2	2·8	6·4
Ethylene dichloride	$TiCl_4$	4·0	43·1	4·2	10·0	42·7

Rearrangement of phenyl esters.

	Phenol	Hydroxy-ketones				Phenol	Hydroxy-ketones		
Ester	(%)	*o* (%)	*p* (%)	*o*/*p*	Ester	(%)	*o* (%)	*p* (%)	*o*/*p*
Acetate	4·2	10·4	76·5	0·15	*iso*Butyrate	6·1	24·6	61·7	0·40
Propionate ...	4·1	16·2	72·4	0·22	Octanoate ...	7·2	29·8	55·5	0·54
n-Butyrate ...	6·8	17·8	72·0	0·25	*iso*Valerate	4·3	23·5	68·1	0·35

For the transformation of certain aliphatic esters of *m*-cresol Coulthard, Marshall, and Pyman [3] stated that the length of the acyl chain had little effect on the *ortho* : *para* ratio

[3] Coulthard, Marshall, and Pyman, *J.*, 1930, 280.

XUM

of products. Baltzly and Bass [4] obtained similar results except that the acetate gave a considerable yield of the *ortho*-isomer. For the phenol series Baltzly, Ide, and Phillips [5] observed that the butyl gave a higher proportion of the *o*-hydroxy-ketone than did the propyl ester, while in his study of 1-naphthyl esters Stoughton [6] reported that the amount of *ortho*-rearrangement decreased in the order acetate, propionate, butyrate, valerate.

While the above results are not strictly comparable, since the experimental conditions varied somewhat, in our experiments with phenyl esters in nitrobenzene solution, catalysed by aluminium chloride, a quantitative study has been made, all products including phenol being accounted for. We have found that the acetate, propionate, *n*-butyrate, and octanoate give chiefly *para*-substitution, but the proportion of *para* decreases and *ortho* increases with the size of the acyl group. We have also observed that replacement of *n*-butyl by *iso*butyl results in an increase in the *ortho* : *para* ratio.

Experimental

Materials.—The esters were dried and fractionally distilled. Phenyl propionate had b. p. 211°, *n*-butyrate 227°, *iso*butyrate 211°, *iso*valerate 235—236°, octanoate 293—294°. The ethylene dichloride was distilled with steam, and dried first over calcium chloride and then phosphoric oxide; the b. p. was 83°.

Rearrangement of Acetates.—(a) *In the absence of solvent.* The ester (0·033 mole) was well mixed with the catalyst (0·052 mole) and heated at 120° for 5 min., then at 165° for 15 min. 5N-Hydrochloric acid was added to the cooled product which was then shaken with nitrobenzene. Sodium hydroxide extracted the *p*- and *o*-hydroxy-ketone and the phenol, the last two compounds being volatile with steam. The latter ketone was converted into its 2 : 4-dinitrophenylhydrazone, in the filtrate from which phenol and *o*- and *m*-cresol were determined by formation of the bromo-derivatives [7,8] and *p*-cresol by the potassium bromate–bromide process.[9] Decomposition occurred in some of these operations, especially with titanium tetrachloride; no ester was recovered in any experiment. The results are shown in Table *a*.

(b) *In nitrobenzene solution.* The ester (0·1 mole) and catalyst (0·2 mole) were heated for 5 hr. at 60°; homogeneous solutions were obtained in all the reactions studied. The products were worked up as described in previous papers of this series. The results are presented in Table *b*.

Rearrangement of Benzoates.—(a) *In the absence of solvent.* The ester (0·033 mole) and catalyst (0·052 mole) were heated at 140° for 15 min., and the products analysed by the method already described. The results are given in Table *c*.

(b) *In nitrobenzene solution.* The ester (0·1 mole), catalyst (0·2 mole), and solvent (100 c.c.) were heated at 60° for 18 hr., the products being separated in the usual way. The results are shown in Table *d*.

Effect of Solvents on the Rearrangement of m-*Tolyl Acetate.*—The ester (0·1 mole) was heated for 24 hr. at 25° with (*a*) anhydrous aluminium chloride (0·2 mole) and (*b*) titanic chloride (0·2 mole) in (*a*) nitrobenzene (100 c.c.) and (*b*) ethylene dichloride (100 c.c.). The products obtained are shown in Table *e*.

Effect of the Acyl Group on the Rearrangement of Phenyl Esters.—The ester (0·1 mole) and catalyst (0·2 mole) in nitrobenzene (100 c.c.) were heated at 50° for 18 hr. Homogeneous solutions were obtained in all reactions; the products were separated and analysed in the usual way, and the results are presented in Table *f*. No ester was recovered in any of the experiments.

Reaction Products.—The following ketones were prepared by rearrangement of the appropriate esters (2 : 4-dinitrophenylhydrazones in parentheses): 2-hydroxyacetophenone (orange needles, m. p. 213° [10]); 4-hydroxyacetophenone,[11] colourless needles (from hot water), m. p.

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[5] Baltzly, Ide, and Phillips, *ibid.*, 1955, **77**, 2522.
[6] Stoughton, *J. Amer. Chem. Soc.*, 1935, **57**, 202.
[7] Cullinane, Evans, and Lloyd, *J.*, 1956, 2222.
[8] Cullinane and Edwards, *J.*, 1958, 434.
[9] *Idem*, *J.*, 1957, 3016.
[10] Johnson, *J. Amer. Chem. Soc.*, 1953, **75**, 2720.
[11] Mozingo, *Org. Synth.*, 1941, **21**, 45.

108° [deep red prisms (from alcohol), m. p. 269° [12]]; 2-hydroxy-3-methylacetophenone [red plates, m. p. 249° (decomp.) [13]]; 4-hydroxy-3-methylacetophenone,[7, 14] colourless plates (from hot water), m. p. 104° [red prisms, m. p. 276° (decomp.) [7]]; 2-hydroxy-4-methylacetophenone [8] [orange-red needles (from ethyl acetate), m. p. 244° [8]]; 4-hydroxy-2-methylacetophenone,[8] colourless needles, m. p. 127° (orange-red needles, m. p. 216° [8]); 2-hydroxy-5-methylacetophenone,[15] colourless needles (from ligroin), m. p. 50° (red prisms, m. p. 271° [9]); 2-hydroxybenzophenone,[16] m. p. 39° (brick-red plates, m. p. 260° [12]); 4-hydroxybenzophenone,[12] m. p. 135° (brick-red needles, m. p. 240° [12]); 4-hydroxy-3-methylbenzophenone,[17] pale yellow needles (from aqueous alcohol), m. p. 173°; 2-hydroxy-4-methylbenzophenone,[17] pale yellow needles (from aqueous alcohol), m. p. 63° (orange-red prisms, m. p. 235° [8]); 4-hydroxy-2-methylbenzophenone,[8] colourless needles, m. p. 129° (red needles, m. p. 224° [8]); 2-hydroxy-5-methylbenzophenone,[18] pale yellow needles (from aqueous alcohol), m. p. 85°; 2-hydroxypropiophenone (red needles, m. p. 189° [19]); 4-hydroxypropiophenone,[20] colourless prisms, m. p. 147—148° (red needles, m. p. 229° [19]); 2-hydroxybutyrophenone [red prisms (from ethyl acetate), m. p. 207° (Found: C, 56·0; H, 4·9; N, 16·2. $C_{16}H_{16}O_5N_4$ requires C, 56·0; H, 4·7; N, 16·3%)]; 4-hydroxybutyrophenone,[21] m. p. 91° [red prisms (from alcohol), m. p. 223° (Found: C, 56·0; H, 4·9; N, 16·2%)]; 2-hydroxy*iso*butyrophenone [red prisms, m. p. 186° (decomp.) [22]]; 4-hydroxy*iso*butyrophenone,[22] m. p. 54° [red needles, m. p. 166° (decomp.) [22]]; 2- (orange-red needles, m. p. 144° [2]), and 4-hydroxyoctanoylbenzene,[2] light brown prisms, m. p. 63° (red needles, m. p. 176° [2]); 2-hydroxy*iso*valerophenone [red plates (from ethyl acetate), m. p. 181° (Found: C, 57·1; H, 5·1; N, 15·4. $C_{17}H_{18}O_5N_4$ requires C, 57·0; H, 5·1; N, 15·6%)]; 4-hydroxy*iso*valerophenone,[23] light brown prisms, m. p. 95—96° [brick-red needles, m. p. 210° (Found: C, 57·0; H, 5·0; N, 15·4%)].

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THE SHANDON LABORATORIES,
UNIVERSITY COLLEGE, CARDIFF.

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597 *Griseofulvin. Part XIII.* Homologues of Griseofulvin and 7-Chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-ene-3 : 2′-dione.*

By L. A. DUNCANSON, JOHN FREDERICK GROVE, and P. W. JEFFS.

The preparation is described of series of homologues of griseofulvin and of the isomer (II; R = Me).

HOMOLOGOUS series of enol ethers (R = alkyl) derived from griseofulvin (I; R = Me) and from the isomer, 7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-ene-3 : 2′-dione (II; R = Me), were required for an investigation of their antifungal activities. The homologues were prepared by alkylation of the trione (III) with the appropriate alcohol in the presence of toluene-*p*-sulphonic acid (method A) or with the requisite diazo-hydrocarbon (method C). Alcoholysis of griseofulvin in the presence of toluene-*p*-sulphonic acid (method B) gave essentially the same results as method A. Method C afforded mixtures of isomeric pairs of

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TABLE 1. *Homologues* (I) *of griseofulvin.*[a]

R	M. p.	$[\alpha]_D^{20}$	Found (%) C	H	Cl	Formula	Required (%) C	H	Cl	Form	Solvent [b]	Yield (%)[c] Method A	B	C
Pr^n	156—157°	+271°	59·5	5·8	8·7	$C_{19}H_{21}O_6Cl$	59·9	5·6	9·3	Plates	MeOH or C_6H_6–Pet B	<1	—	19[f]
Bu^n	155	+263	60·85	5·9	—	$C_{20}H_{23}O_6Cl$	60·8	5·9	9·0	Prisms	MeOH	<1	7	42[e]
Bu^i	135—136	+264	60·75	5·8	—	$C_{20}H_{23}O_6Cl$	60·8	5·9	—	Needles	Pet A	—	25	—
n-C_5H_{11}	154	+254	61·7	6·3	—	$C_{21}H_{25}O_6Cl$	61·7	6·2	—	Prisms	MeOH	9	—	30[d]
n-C_6H_{13}	161	+248	62·5	6·2	8·6	$C_{22}H_{27}O_6Cl$	62·5	6·4	8·4	Prisms	C_6H_6–Pet	19	—	—
n-C_7H_{15}	159—160	+242	62·8	6·6	8·15	$C_{23}H_{29}O_6Cl$	63·2	6·7	8·1	Prisms	,,	7	—	—
n-C_8H_{17}	134	+237	64·1	7·0	7·9	$C_{24}H_{31}O_6Cl$	63·9	6·9	7·9	Plates	MeOH	11	—	—
										Prisms	C_6H_6–Pet			
n-$C_{10}H_{21}$	91	+217	65·0	7·6	7·4	$C_{26}H_{35}O_6Cl$	65·2	7·4	7·4	Prisms	MeOH	5	—	—
n-$C_{16}H_{31}$	89—91	+184	67·4	8·05	5·9	$C_{31}H_{45}O_6Cl$	67·8	8·3	6·45	Prisms	Et_2O–Pet or EtOH	—	—	7[d,f]

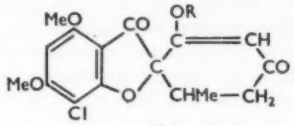
[a] $\lambda_{max.}$ 236, ~260, 292, 325—6 mμ (log ε 4·3—4·4, 4·1—4·2, 4·3—4·4, 3·7—3·8 respectively); accurate values for ε are available. For ethers (I and II; R = Et) see Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3979. [b] Pet = light petroleum, Pet A, b. p. 40—60°, Pet B, b. p. 60—80°. [c] 30% in Et_2O, 20% in Et_2O–Bu^nOH. [d] None of the isomer (II). [e] Calc. on trione converted. [f] in ethyl ether.

TABLE 2. *Homologues* (II).

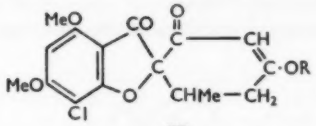
R	M. p.	$[\alpha]_D^{20}$	Found (%)[a] C	H	Cl	Form	Solvent	$\lambda_{max.}$ log ε				Yield (%)[d] Method A	B	C
Pr^n	179°	+196°	59·9	5·7	9·0	Prisms	MeOH	234	263	292	325	29	—	13[e]
								4·32	4·33	4·36	3·74			
Pr^i	188—190	+208	60·2	5·6	9·3	Needles	,,	234	265	292	325	80[e]	—	—
								4·28	4·35	4·31	3·70			
Bu^n	157—158	+192	61·1	5·8	9·0	Needles	,,	234	264	293	325	60	40	0[f]
								4·32	4·33	4·32	3·80			
Bu^i	152—155	+212	61·2	5·8	—	Prisms	,,	236	267	292	326	—	57	—
								4·31	4·36	4·32	3·75			
sec.-Bu	210—211	+210	60·75	6·2	9·0	Needles	EtOH	235	268	292	325	—	88[e]	—
								4·28	4·37	4·32	3·73			
n-C_5H_{11}	143—144	+197	61·7	6·3	—	Needles	MeOH	235	265	292	326	66	—	0
								4·32	4·32	4·31	3·66			
n-C_6H_{13}	117—118	+195	62·5	6·5	8·3	Prisms	EtOH	234	264	292	326	62	—	—
								4·31	4·34	4·31	3·71			
cyclo-C_6H_{11}	208—210	+171	62·3	6·0[b]	—	Plates	MeOH	235	269	292	325	73[e]	—	—
								4·30	4·39	4·33	3·76			
n-C_7H_{15}	120—122	+193	63·1	6·6	7·8	Needles	EtOH	235	265	293	326	29	—	—
								4·31	4·32	4·30	3·72			
n-C_8H_{17}	129	+179	64·1	7·0	—	Needles	,,	234	265	293	326	55	—	—
								4·28	4·30	4·29	3·72			
n-$C_{10}H_{21}$	84—86	+169	65·5	7·5	7·4	Prisms	EtOH or Pet	235	265	293	326	40	—	—
								4·34	4·35	4·33	3·76			

[a] For required % see Table 1. Required: C, 62·8; H, 6·0%. [b] $C_{22}H_{25}O_6Cl$. [c] Ethanolate, m. p. 96—98°, needles from ether–ethanol (Found: C, 59·8; H, 6·4. $C_{26}H_{33}O_6Cl,C_2H_5{\cdot}OH$ requires C, 59·9; H, 6·6%). [d] Calc. on trione converted. [e] None of the isomer (I). [f] 3% in Et_2O, 20% in Et_2O–Bu^nOH. [g] in ethyl ether.

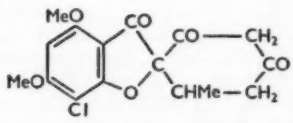
homologues of (I and II; R = Me) [1,2] which were separated by chromatography and were distinguished by their ultraviolet spectra.[2] Method A [3] yielded predominantly homologues of compound (II; R = Me), and for steric reasons this was most marked with secondary alcohols. With primary alcohols some formation of griseofulvin homologues took place but the *n*-propyl, *n*-butyl, and *n*-pentyl compounds were only obtained in good



(I)

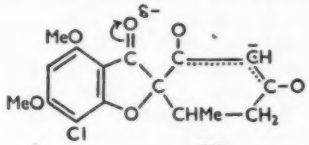


(II)

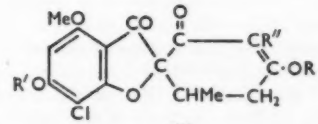


(III)

yield by method C using the diazo-hydrocarbon [4] in toluene. When the diazo-hydrocarbon was used in ether, or in ether in the presence of the alcohol, the yield of the griseofulvin homologue was lower and that of the homologue (II) progressively higher. Polarisation of the 3-carbonyl group may be a factor in determining the location of the negative charge in the mesomeric anion (IV): this polarisation will be a minimum and reaction at the 4′-position least favoured in a solvent such as toluene.



(IV)



(V)

The *n*-butyl homologues (I and II; R = Bu), prepared from (III) and diazobutane, were accompanied in low yield by the *C*-*n*-butyl derivative (V; R′ = Me, R = R″ = Bu^n). The structure was deduced from the optical rotation, which was characteristic of a compound (II) and from the ultraviolet spectrum. The latter showed a bathochromic shift of ~20 mμ, compared with (II; R = Bu^n), of the 263 mμ 1 : 3-dione enol-ether chromophore peak and caused this to overlap the coumaranone chromophore peak at 292 mμ giving a single broad band with maximum at 285 mμ. This shift is to be expected of a 3′-alkyl substituent by analogy with dimedone ethyl enol ether ($\lambda_{max.}$ 250 mμ) and the 2-methyl derivative ($\lambda_{max.}$ 268 mμ).[5] 6 : 4′-Di-*n*-butoxy-7-chloro-4-methoxy-6′-methylgris-3′-ene-3 : 2′-dione (V; R = R′ = Bu^n, R″ = H), from diazobutane and 7-chloro-6-hydroxy-4-methoxy-2′-methylgrisan-3 : 4′ : 6′-trione, had the ultraviolet spectrum characteristic of a compound (II).

Homologues (II) derived from secondary alcohols showed a small bathochromic shift and intensification of the 263 mμ band (Fig. 1 and Table 2) compared with homologues derived from normal primary alcohols: these effects were most pronounced for the *cyclo*hexyl ether. They were not observed when the spectra of the ethyl and *iso*propyl ($\lambda_{max.}$ 252 mμ) enol ethers of dimedone were compared; they are due, presumably, to steric enhancement of the interaction [6] in this series between the coumaranone and 1 : 3-dione enol ether chromophores.

[1] Oxford, Raistrick, and Simonart, *Biochem. J.*, 1939, **33**, 240.
[2] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3949.
[3] Frank and Hall, *J. Amer. Chem. Soc.*, 1950, **72**, 1645.
[4] Adamson and Kenner, *J.*, 1937, 1551.
[5] Meek, Turnbull, and Wilson, *J.*, 1953, 2891.
[6] Duncanson, Grove, MacMillan, and Mulholland, *J.*, 1957, 3555.

XUM

The specific optical rotations (Fig. 2) of the homologues (I) and (II) were inversely proportional to the number of carbon atoms in R.[7]

Condensation of the trione (III) with tetra-*O*-acetyl-α-D-glucosidyl bromide [8] gave a tetra-acetylglucoside shown to have the structure (I; R = $C_6H_7O_5Ac_4$) by the ultraviolet spectrum. Attempted hydrolysis of the acetyl residues with methanolic ammonia [9] or by Zemplén's method [10] failed.

The antifungal activities of the homologues will be reported elsewhere.

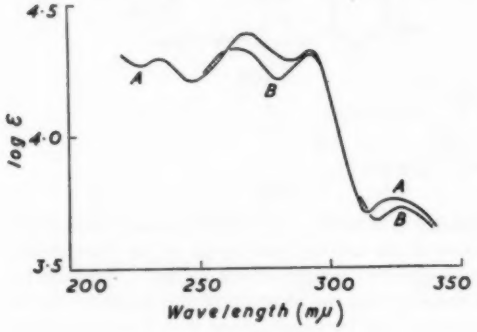


FIG. 1. *Ultraviolet absorption spectra of compounds* (II): *A*, R = cyclo*hexyl*; *B*, R = n-*hexyl*.

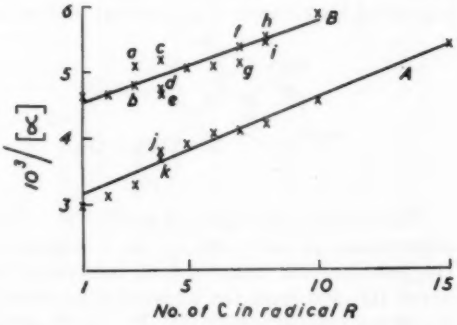


FIG. 2. *Relation of* $[\alpha]_D^{20}$ *to number of carbon atoms in the radical* R.

A, (I; R = alkyl). *B*, (II; R = alkyl).

a, Pr^n. *b*, Pr^i. *c*, Bu^n. *d*, Bu^s. *e*, Bu^i. *f*, *n*-C_7H_{15}. *g*, (V; R = R′ = Bu^n, R″ = H). *h*, *n*-C_8H_{17}. *i*, (V; R′ = Me, R = R″ = Bu^n). *j*, Bu^n. *k*, Bu^i.

EXPERIMENTAL

M. p.s are corrected. Microanalyses are by W. Brown. In chromatography B.D.H. alumina was rendered alkali-free (pH 4) and activated at 250°/15 mm. for 2 hr. Ultraviolet spectra were determined for EtOH solutions with a Unicam S.P. 500 spectrophotometer. Optical rotations were determined in acetone (*c* 1·0).

Preparation of the Enol Ethers.—(A) *Method of Frank and Hall.*[3] The trione (III) (0·5 g.), toluene-*p*-sulphonic acid (0·025 g.) and the alcohol (3 mol.) in benzene were heated under reflux in a flask fitted with a Dean and Stark separator, water being removed as formed. The reflux was arranged so that the distillate consisted chiefly of aqueous benzene; this condition was not quite fulfilled when propan-1- and -2-ol were used and small amounts of these alcohols were added from time to time. The benzene could be omitted for alcohols higher than C_5. After 6 hr. the benzene and alcohol were removed *in vacuo*. The residual gum in ether was washed with aqueous sodium hydrogen carbonate, recovered, and chromatographed (see below).

(B) *Alcoholysis of griseofulvin.* Griseofulvin (0·5 g.) and toluene-*p*-sulphonic acid (0·025 g.) were heated under partial reflux with the alcohol (25 ml.) for 12 hr. The rate of take off was 1 ml. per hr. and the volume was maintained by the addition of fresh alcohol. After removal of the alcohol *in vacuo* the residual gum was chromatographed.

[7] Gerson, *Nature*, 1957, **179**, 310.
[8] Fisher, Hawkins, and Hibbert, *J. Amer. Chem. Soc.*, 1940, **62**, 1412.
[9] Lucas, *Bull. Soc. chim. France*, 1935, **2**, 1605.
[10] Zemplén and Pacsu, *Ber.*, 1929, **62**, 1613.

(C) *Diazo-hydrocarbon method.* The trione (III) (0·35 g.), suspended in toluene (50 ml.) at 0°, was treated with an excess (*ca.* 2 mol.) of the diazo-hydrocarbon in toluene. (The diazo-hydrocarbon, prepared according to Adamson and Kenner's directions,[4] was distilled into toluene in a cold trap.) After 3 days at room temperature with frequent shaking, the toluene and excess diazo-hydrocarbon were removed *in vacuo* and the residual gum in ether was washed with sodium hydrogen carbonate solution, recovered, and chromatographed.

Diazopentadecane, prepared by the action of methanolic potassium hydroxide on methyl *N*-nitrosopentadecylcarbamate (from methyl pentadecylcarbamate [11] and nitrous fumes in ether), was used in ether without purification.

The *N-nitroso-derivative* from 1-aminopentane and synthetic (±)-pulegone formed needles, m. p. 112—113° [from light petroleum (b. p. 40—60°)] (Found: C, 67·4; H, 10·1; N, 10·9. $C_{15}H_{28}O_2N_2$ requires C, 67·1; H, 10·5; N, 10·4%). Adamson and Kenner [4] give m. p. 88·5° for the nitroso-derivative from (+)-pulegone.

Chromatography of the Crude Mixed Enol Ethers.—The gum (400 mg.) in benzene was chromatographed on alumina (30 × 1·8 cm.) in ultraviolet light, and the column was eluted consecutively with benzene–light petroleum (b. p. 60—80°) (4 : 1), benzene, benzene–ether (99 : 1, then 9 : 1), and benzene–methanol (1000 : 1, then 200 : 1). Benzene–ether (99 : 1) usually effected the complete separation on the column of two blue fluorescent bands and elution with this solvent was continued until the lower band (containing the homologue (II) had been removed. Benzene–methanol (200 : 1) brought out the upper band which contained the homologue (I). Physical constants, analytical data, and yields of the new *compounds* are given in Tables 1 and 2.

4′-n-Butoxy-3′-n-butyl-7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-ene-3 : 2′-dione (V; R′ = Me, R = R″ = Bu^n).—Chromatography of the product from the trione (III) and diazobutane in ether or toluene revealed a third blue fluorescent band intermediate between the two principal bands. Elution with benzene–ether (9 : 1) furnished *4′-n-butoxy-3′-n-butyl-7-chloro-4 : 6-dimethoxy-6′-methylgris-3′-ene-3 : 2′-dione* (35 mg., 7%), prisms, m. p. 214—216° (from ether or methanol), $[\alpha]_D^{26}$ +180° (Found: C, 63·8, 64·2; H, 7·0, 7·0; Cl, 7·7, 8·2. $C_{34}H_{51}O_6Cl$ requires C, 63·9; H, 6·9; Cl, 7·9%), $\lambda_{max.}$ ~234, 285, 327 mμ (log ε 4·24, 4·40, 3·77 respectively).

6 : 4′-Di-n-butoxy-7-chloro-4-methoxy-6′-methylgris-3′-ene-3 : 2′-dione (V; R = R′ = Bu^n, R″ = H).—7-Chloro-6-hydroxy-4-methoxy-2′-methylgrisan-3 : 4′ : 6′-trione (0·50 g.), suspended in methanol (2 ml.), was treated with excess of ethereal diazobutane. Chromatography of the product gave needles [from benzene–light petroleum (b. p. 40—60°)], m. p. 136°, of *6 : 4′-di-n-butoxy-7-chloro-4-methoxy-6′-methylgris-3′-ene-3 : 2′-dione* (227 mg., 34%), $[\alpha]_D^{26}$ +185° (Found: C, 63·3; H, 6·7. $C_{23}H_{29}O_6Cl$ requires C, 63·2; H, 6·7%), $\lambda_{max.}$ 235, 265, 292, 325 mμ (log ε 4·33, 4·32, 4·32, 3·72 respectively).

Dimedone iso*Propyl Enol Ether.*—Dimedone (7 g.), toluene-*p*-sulphonic acid (0·2 g.) and propan-2-ol (11 g.) were heated in benzene (100 ml.) (method A) for 10 hr. The iso*propyl ether* crystallised from light petroleum (b. p. 40—60°) in prisms (2·7 g.), m. p. 47° (Found: C, 72·7; H, 9·9. $C_{11}H_{18}O_2$ requires C, 72·5; H, 10·0%), $\lambda_{max.}$ 252 mμ (ε, 18,100).

Tetra-O-acetyl-α-D-glucoside of the Trione (III) (with Dr. T. P. C. Mulholland).—Tetra-*O*-acetyl-α-D-glucosidyl bromide (4·85 g.) in acetone was added with stirring to the trione (III) (3·88 g.) in acetone (25 ml.) containing 0·93N-potassium hydroxide (12·3 ml.) at 5°. The pH was maintained at *ca.* 9 by further addition of potassium hydroxide (30 ml.) during 45 min. and the solution was kept for 4 days at room temperature, filtered and concentrated *in vacuo* at 30°. The acetone-soluble portion of the residual gum was dissolved in ether and extracted with sodium hydrogen carbonate. Unchanged trione (2·2 g.) was recovered from the acidic fraction. Slow evaporation of the dried neutral ethereal solution furnished needles (532 mg.), m. p. 122—130°. Recrystallisation from ether–methanol gave the *tetra-O-acetylglucoside*, needles, m. p. 128—134°, $[\alpha]_D^{17}$ +140° (*c* 1·09 in MeOH) (Found: C, 53·7; H, 5·0; Cl, 5·3. $C_{30}H_{33}O_{15}Cl$ requires C, 53·85; H, 5·0; Cl, 5·3%), $\lambda_{max.}$ ~235, ~258, 294, ~325 mμ (log ε 4·35, 4·07, 4·38, 3·77 respectively).

We thank Mr. D. Gardner and Mr. S. C. Bishop for technical assistance.

Imperial Chemical Industries Limited, Akers Research Laboratories,
The Frythe, Welwyn, Herts. [*Received, March 17th*, 1958.]

[11] Jeffreys, *Ber.*, 1897, **30**, 898.

XUM

598. *The Hydrolysis of Simple Amides catalysed by Carboxylic Acids.*

By K. G. Wyness.

The hydrolysis of amides in nearly neutral, buffered solutions of acetic acid at 220° shows kinetic dependence upon the concentration of carboxylic acid molecules. Consideration of structural, solvent, and deuterium-isotope effects suggests that the catalysis involves anhydride formation from the acetate ion and the amide conjugate acid, with subsequent rapid hydrolysis of the anhydride.

The possibility of catalysis in substitutions at a carbonyl-carbon atom by species other than the hydrogen and hydroxyl ion has frequently been discussed.[1-5] Recent work has focused attention on general base-catalysed hydrolysis of phenyl esters [3] and carboxylic anhydrides.[4] The only example of apparent general acid-catalysis in the hydrolysis of amides has recently been reported by Bender,[5] who found that the hydrolysis of phthalamic acid was subject to intramolecular catalysis by the un-ionised carboxyl group.

Although it has usually been assumed that with intermolecular catalysis amide hydrolysis is specifically hydrogen- and hydroxide-ion-catalysed, work reported here on the hydrolysis of simple *N*-substituted amides at 220° in buffered solutions of acetic acid shows that part of the hydrolysis is a reaction of the kinetic form $v = k[\mathrm{HA}][\mathrm{amide}]$, indicating an apparent catalysis by the un-ionised carboxyl group.

TABLE 1. *Hydrolysis of* N-n-*butylacetamide at* 220° *in buffered aqueous solutions.*

Concentrations are uncorrected for the expansion of the solvent.

Ionic strength	AcOH (M)	NaOAc (M)	NaCl (M)	Acid/ Buffer	pH *	10^5k (sec.$^{-1}$)	10^5k_{HA}
0·016	0·0128	0·0025	0·0135	5·15	5·0	1·11	
,,	0·0274	0·0053	0·0107	,,	,,	1·30	
,,	0·0408	0·0079	0·0081	,,	,,	1·46	
,,	0·0516	0·0100	0·0060	,,	,,	1·60	
,,	0·0633	0·0123	0·0037	,,	,,	1·74	
,,	0·0799	0·0155	0·0	,,	,,	1·94	12·3
0·062	0·0146	0·0042	0·0578	3·45	5·2	1·19	
,,	0·0350	0·0101	0·0519	,,	,,	1·50	
,,	0·0490	0·0142	0·0478	,,	,,	1·60	
,,	0·0639	0·0185	0·0435	,,	,,	1·80	
,,	0·0770	0·0223	0·0397	,,	,,	2·02	
,,	0·0808	0·0234	0·0386	,,	,,	2·07	
,,	0·0993	0·0288	0·0332	,,	,,	2·23	12·3
0·150	0·0271	0·0262	0·1238	1·04	5·7	1·25	
,,	0·0301	0·0290	0·1210	,,	,,	1·46	
,,	0·0558	0·0538	0·0962	,,	,,	1·65	
,,	0·0714	0·0690	0·0810	,,	,,	2·06	
,,	0·1095	0·1059	0·0441	,,	,,	2·47	
,,	0·1113	0·1075	0·0425	,,	,,	2·11	
,,	0·1357	0·1310	0·0190	,,	,,	2·53	
,,	0·1360	0·1315	0·0185	,,	,,	2·65	12·3

* Values calculated for a temperature of 218° by using K_a(acetic acid) $= 1·72 \times 10^{-5}$, determined by Noyes and Cooper (*J. Amer. Chem. Soc.*, 1908, **30**, 193).

Table 1 shows first-order rate constants obtained for the hydrolysis of *N*-*n*-butylacetamide in acetic acid–sodium acetate buffer solutions of constant pH and ionic strength.

[1] Dawson and Lowson, *J.*, 1927, 2444; 1929, 393; Dawson, Pycock, and Spivey, *J.*, 1933, 291.
[2] Rolfe and Hinshelwood, *Trans. Faraday Soc.*, 1934, **30**, 935; Hinshelwood and Legard, *J.*, 1935, 587.
[3] Bender and Turnquest, *J. Amer. Chem. Soc.*, 1957, **79**, 1652, 1656.
[4] Gold and Jefferson, *J.*, 1953, 1409.
[5] Bender, *J. Amer. Chem. Soc.*, 1957, **79**, 1258.

XUM

In an aqueous solution of an amide containing an acid HA, buffered by its anion A^-, the observed first-order rate constant of hydrolysis is given by the general expression: [6]

$$k = k_0 + k_{H^+}[H^+] + k_{OH^-}[OH^-] + k_{HA}[HA] + k_{A^-}[A^-]$$

At constant pH this equation reduces to:

$$k = \text{Constant} + k_{HA}[HA] + k_{A^-}[A^-]$$
$$= \text{Constant} + [HA]\{k_{HA} + k_{A^-}[A^-]/[HA]\}$$

so that a plot of k against the acid concentration [HA] should be linear, of slope $k_{HA} + k_{A^-}[A^-]/[HA]$. The last column of Table 1 shows values of this slope for different values of the buffer ratio $[A^-]/[HA]$. The constancy of these figures indicates that k_{A^-} is sensibly zero and that the observed catalysis is due only to the un-ionised acid HA, or to its ions acting together.

At least three possible mechanisms fitting this kinetic form can be written for the catalysis. The first is represented by the classic mechanism of general acid-catalysis, involving rate-determining proton-transfer from the carboxylic acid to the amide without the intervention of solvent.[7] The resulting amide conjugate acid is then rapidly hydrolysed by a water molecule.

Mechanism I:

$$CH_3{\cdot}CO_2H + R'{\cdot}CO{\cdot}NHR \xrightarrow{k_1} R'{\cdot}CO{\cdot}NH_2R^+ + CH_3{\cdot}CO_2^- \text{ (slow)}$$
$$R'{\cdot}CO{\cdot}NH_2R^+ + H_2O \longrightarrow \text{Products (fast)}$$
$$\therefore \text{Rate} = k_1[CH_3{\cdot}CO_2H][R'{\cdot}CO{\cdot}NHR]$$

This process is most improbable on grounds of general chemical experience since it involves slow proton-transfer from an oxygen to a nitrogen atom, and fast fission of a strong C–N bond. The lack of marked solvent effect (Table 2) shows that the rate-determining step

TABLE 2. *Effect of solvent polarity and ionic strength on the catalytic constant.*

Solvent	Ionic strength	$10^5 k_{HA}$
H_2O–dioxan (67% H_2O)	0·024	6·80
H_2O	0·016	12·3
H_2O	0·062	12·3
H_2O	0·150	12·3

TABLE 3. *The effect of structure. Relative catalytic constants in 67% aqueous dioxan.*

$CH_3{\cdot}CO{\cdot}NHR$	R =	Ph	H	Me	Et	Bu^n	Pr^i	Bu^t
	k_{HA} =	1·7	4·2	1·2	1	0·85	0·47	0·51
$R'{\cdot}CO{\cdot}NHBu^n$	R′ =		H	Me	Et	Pr^i	Bu^t	
	k_{HA} =		4·0	0·85	0·62	0·24	0·066	

is not one in which ions are produced, while structural changes in R and R′ (Table 3) * show that increased basicity at the amide nitrogen atom does not accelerate the reaction, as the mechanism would require.

The second mechanism is of the type suggested by Bender [5] for the hydrolysis of phthalamic acid. This is essentially a proton-catalysed nucleophilic carbonyl substitution, rather than a true general acid-catalysis, since the acetate ion acts as a nucleophilic reagent rather than as a base. The products of the rate-determining step would be the anhydride and the amine, with subsequent rapid hydrolysis of the anhydride.

* The comparative rates quoted in Table 3 were measured in aqueous dioxan because some of the amides used were insoluble in water. The actual rate constants are tabulated in the Experimental section.

[6] Bell, " Acid-base Catalysis," Oxford, 1941, p. 60.
[7] Ref. 6, p. 124.

XUM

Mechanism II:

$$CH_3{\cdot}CO_2H \underset{K_{HOAc}}{\rightleftharpoons} CH_3{\cdot}CO_2^- + H^+$$

$$H^+ + R'{\cdot}CO{\cdot}NHR \rightleftharpoons R'{\cdot}CO{\cdot}NH_2R^+ \text{ (pre-equilibrium)}$$

$$CH_3{\cdot}CO_2^- + R'{\cdot}CO{\cdot}NH_2R^+ \xrightarrow[k_2]{} CH_3{\cdot}CO{\cdot}O{\cdot}OC{\cdot}R' + NH_2R \text{ (slow)}$$

$$\downarrow H_2O \text{ (fast)}$$

$$CH_3{\cdot}CO_2H + R'{\cdot}CO_2H$$

$$\text{Rate} = k_2 \,.\, (K_{HOAc}/K_{SH^+})[CH_3{\cdot}CO_2H][R'{\cdot}CO{\cdot}NHR]$$

where K_{SH^+} is the dissociation constant of the amide conjugate acid.

The third possible mechanism involves hydrogen-bonded complex-formation between the amide and the carboxylic acid group, in equilibrium with the uncomplexed molecules. Such complexes may be more easily hydrolysed than the amide itself, by a mechanism similar to that suggested for esterification,[8] where, under certain conditions, catalysis by carboxyl groups is indicated.[2]

Mechanism III:

$$CH_3{\cdot}CO_2H + R'{\cdot}CO{\cdot}NHR \underset{K_{H\text{-bond}}}{\rightleftharpoons} CH_3{\cdot}CO_2H{-}R'{\cdot}CO{\cdot}NHR \text{ (pre-equilibrium)}$$

$$CH_3{\cdot}CO_2H{-}R'{\cdot}CO{\cdot}NHR + H_2O \xrightarrow[k_3]{} \text{Products (slow)}$$

$$\text{Rate} = k_3 \,.\, K_{H\text{-bond}}[CH_3{\cdot}CO_2H][R'{\cdot}CO{\cdot}NHR]$$

Both mechanisms II and III have ambiguous polar requirements, owing to their two-stage nature. Both are therefore consistent with the observed insensitivity of the reaction to changes in R (Table 3). The effect of successive α-methyl substitution in R′ is also that expected for bimolecular attack at the carbonyl-carbon atom, showing marked steric hindrance with increasing bulk in this substituent. A more discriminating test of mechanism, however, is provided by the effect of deuterium substitution.

In mechanism II the ratio of rates in H_2O and D_2O is given by

$$(k_H/k_D)_{HOAc} = (k_2)_H/(k_2)_D \,.\, K_{HOAc}/K_{DOAc} \,.\, K_{SD^+}/K_{SH^+}$$

The constant k_2, for nucleophilic attack by acetate ion on the amide conjugate acid, is expected to have a negligible isotope effect. K_{HOAc}/K_{DOAc} has the value 3·3 at 25°.[9] K_{SD^+}/K_{SH^+} for *N*-*n*-butylacetamide can be obtained by interpolation on the curve obtained by Rule and LaMer [9] relating this ratio to the dissociation constant of the proto-acid. For *N*-*n*-butylacetamide the latter has the value $pK_{SH^+} = 0{\cdot}15$,[10] and $K_{SD^+}/K_{SH^+} = 0{\cdot}55$. At 25° therefore, mechanism II affords a ratio $(k_H/k_D)_{HOAc} = 3{\cdot}3 \times 0{\cdot}55 = 1{\cdot}8$. If we can assume that an increase in temperature will not greatly affect the relative magnitudes of the dissociation constant ratios then the final ratio of approximately 1·8 will hold also at 220°.

The rate-constant ratio for mechanism III is given by

$$(k_H/k_D)_{HOAc} = (k_3)_H/(k_3)_D{\cdot}K_{H\text{-bond}}/K_{D\text{-bond}}$$

Information on the relative strengths of hydrogen and deuterium bonds is scanty, but it has been suggested [11] that the deuterium bond is slightly the more stable, so that $K_{H\text{-bond}}/K_{D\text{-bond}} < 1$. The change in k_3 on deuterium substitution is likely to be due almost entirely to the lower basicity of D_2O than of H_2O. In the hydrolysis of acetamide in concentrated acid, where it is assumed that most of the substrate is in the

[8] Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 701.
[9] Rule and LaMer, *J. Amer. Chem. Soc.*, 1938, **60**, 1981.
[10] Goldfarb, Mele, and Gutstein, *ibid.*, 1955, **77**, 6194.
[11] Hawthorne, *ibid.*, 1954, **76**, 6358; Herman and Hofstadter, *J. Chem. Phys.*, 1938, **6**, 534.

XUM

conjugate acid form,[12] the rate ratio should be a reliable measure of the nucleophilic power of D_2O relative to H_2O. The published[13] ratio, for 4N-acid at 25°, is 1·16. Since at higher temperatures the isotope effect becomes smaller, the final ratio $(k_H/k_D)_{HOAc}$ cannot be far from unity at 220°.

It is noted, for completeness, that the reaction by mechanism I is also expected to suffer a decrease in rate on substitution of solvent D_2O for H_2O. If we can assume that the difference in zero-point energy between the transition states for proton- and deuteron-transfer is unlikely to be large enough to affect appreciably the ratio of the rates in D_2O and H_2O, then we expect a value for $(k_H/k_D)_{HOAc}$ close to the theoretical maximum. This can be calculated from experimentally determined values for O–H(D) bond-stretching frequencies in acetic and deuteroacetic acid,[14] and a value $(k_H/k_D)_{HOAc} = 3·1$ results for a temperature of 220°.

Table 4 shows results obtained from a series of runs in D_2O. The value of k_{DA} obtained yields a ratio $(k_H/k_D)_{HOAc} = 2·0$.

TABLE 4. *Hydrolysis of* N-n-*butylacetamide at* 220° *in* D_2O, *catalysed by deuteroacetic acid.*

Ionic strength	AcOD (M)	AcONa (M)	NaCl (M)	Acid/ Buffer	10^5k (sec.$^{-1}$)	10^5k_{DA}	$(k_H/k_D)_{HA}$
0·0186	0·0218	0·0055	0·0131	4·0	0·69		
,,	,,	,,	,,	,,	0·72		
,,	0·0366	0·0092	0·0094	,,	0·86		
,,	0·0574	0·0144	0·0042	,,	1·01		
,,	0·0743	0·0186	0·0	,,	1·07		
0·019	0·0911	0·0194	,,	4·7	1·13		
0·030	0·1139	0·0296	,,	,,	1·27	6·12	2·0

The isotope effect therefore supports mechanism II. Structural and solvent effects are consistent with this reaction path, which is the same as that suggested by Bender [5] for the carboxylic acid-catalysed hydrolysis of phthalamic acid. Although this author has concluded that such an interaction between the carboxyl and the amide group occurs only intramolecularly, the present observations suggest that this is not necessarily the case.

EXPERIMENTAL

Materials.—The amides listed below were prepared by treating the corresponding amine with the carboxylic acid, anhydride, or chloride, and were purified by distillation at reduced pressure. *N*-Ethyl-, b. p. 140—141°/91 mm., *N*-*n*-propyl-, b. p. 112°/14 mm., *N*-*n*-butyl-, b. p. 121—122°/13 mm., and *N*-*iso*propyl-acetamide, b. p. 89—90°/9 mm.; *N*-*n*-butyl-propionamide, b. p. 122°/11 mm., -*iso*butyramide, b. p. 124—126°/12 mm., and -αα-dimethylpropionamide, b. p. 114°/12 mm.; *N*-*tert.*-butylacetamide was recrystallised from hexane and had m. p. 99°. The following amides were recrystallised from commercial products: acetamide, m. p. 81°; acetanilide, m. p. 115°; benzamide, m. p. 129°. " AnalaR " acetic acid and anhydrous sodium acetate were used without further purification. Dioxan was purified by distilling it from stannous chloride to remove peroxides, refluxing it over sodium for 12 hr, and redistilling it. The fraction boiling at 100°/760 mm. was collected.

Method.—Buffered solutions were prepared by adding a known quantity of standard sodium hydroxide solution to a solution of acetic acid. Successive dilution with a sodium chloride solution of concentration equal to that of the acetate provided a series of solutions of constant pH and ionic strength, differing only in concentration of acid and buffer. For runs in aqueous dioxan and in deuterium oxide, solid anhydrous sodium acetate was used to buffer the acid. Stock solutions prepared in this way were used to make up final mixtures by addition to the amide (usually about 0·3M), which was weighed accurately into volumetric flasks. Solutions

[12] Ref. 6, p. 148.
[13] Reitz, *Z. phys. Chem.*, 1939, *A*, **183**, 371.
[14] Wilmshurst, *J. Chem. Phys.*, 1956, **25**, 1171.

in deuterium oxide were prepared in a dry-box. The concentrations of the buffer constituents in the final solutions were determined by titration.

1 ml. quantities of the amide solution were pipetted into small ampoules constructed from resistance glass tubing of 4 mm. bore. These were sealed under nitrogen and ten or twelve were immersed together in an electrically heated silicone-oil bath controlled by a mercury-in-glass regulator and electronic relay within $\pm 0{\cdot}1°$. Tubes were taken out at intervals and quenched in cold water. The extent of hydrolysis was measured by titrating the amine produced, in 68 : 32 w/w phenol–methanol, with methanolic 0·05N-hydrochloric acid, to thymol-blue. The total titre was the sum of that due to amine and that corresponding to the sodium acetate used as buffer. The latter was determined separately from the initial reaction mixture. First-order rate constants were determined graphically, the final extent of reaction (about 10%) being small enough for the reverse amidation to remain negligible.

The following are details of a typical run. 0·345N-*N*-*n*-Butylacetamide was hydrolysed at 220° in aqueous solution 0·0408N in acetic acid and 0·0079N in sodium acetate, the total ionic strength being made up to 0·016 with sodium chloride. 5 ml. samples were titrated, after reaction, in phenol–methanol with 0·0474N-hydrochloric acid. The control titre corresponding to the constant sodium acetate concentration was 0·80 ml. The rate constants are in this case integrated values (see Table).

Time (min.)	0	10	20	30	40	50	60	70	80	90	100	110	120
Titre, less control (extent of reaction expressed as ml. of 0·0474N-acid)	0	0·30	0·62	0·98	1·30	1·60	1·86	2·16	2·53	2·78	3·04	3·32	3·64
10^5k (sec.$^{-1}$)	—	1·38	1·43	1·52	1·48	1·50	1·45	1·45	1·48	1·47	1·43	1·45	1·47

For comparison of k_{HA} in different amides, 67 : 33 v/v water–dioxan was used as solvent owing to the insolubility of some of the amides in pure water. The catalytic constants shown below were calculated in each case from the slope of the graph of total rate constant k against acetic acid concentration, which varied from 0·03N to 0·16N. The ratio of acid to buffer was 6·8, and the ionic strength 0·024, throughout. Not less than 4, and usually 5 or 6, points were used to define the straight line.

Amide	$BzNH_2$	$AcNH_2$	AcNHMe	AcNHEt	AcNHPr^n
10^5k_{HA}	3·51	34·1	9·36	8·07	6·93
Amide	AcNHPr^i	AcNHBu^t	AcNHPh	$AcNEt_2$	H·CO·NHBu^n
10^5k_{HA}	3·81	4·08	13·6	6·15	32·0
Amide	AcNHBu^n	Et·CO·NHBu^n	Pr^i·CO·NHBu^n	Bu^t·CO·NHBu^n	
10^5k_{HA}	6·80	4·97	1·90	0·536	

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Pontypool, Mon.

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XUM

599. *Organometallic and Organometalloidal Fluorine Compounds. Part XIV.* Trifluoromethyl Derivatives of Selenium.†*

By J. W. Dale, H. J. Emeléus, and R. N. Haszeldine.

Trifluoroiodomethane and selenium at 260—285° give bistrifluoromethyl selenide, $(CF_3)_2Se$, and the diselenide, $(CF_3)_2Se_2$. The latter decomposes in ultraviolet light to the monoselenide and selenium; these compounds do not form addition products with mercuric chloride or alkyl iodides. The monoselenide is stable and resistant to hydrolysis. Chlorination of the selenide or diselenide gives trifluoromethylselenenyl chloride, $CF_3{\cdot}SeCl$, and trifluoromethylselenium trichloride, $CF_3{\cdot}SeCl_3$. A monobromide is formed similarly. Oxidation of the diselenide with nitric acid, or hydrolysis of the trichloride, yields the strong monobasic trifluoromethylseleninic acid, $CF_3{\cdot}SeO_2H$. The diselenide with mercury in ultraviolet light gives bis(trifluoromethylseleno)-mercury, $(CF_3{\cdot}Se)_2Hg$, which is also obtained by shaking trifluoromethylselenenyl chloride with mercury. The mercurial and anhydrous hydrogen chloride give the hydrogen selenide, $CF_3{\cdot}SeH$. These compounds are compared with their alkyl and aryl analogues.

Direct reaction of trifluoroiodomethane with certain metals and non-metals has been applied in preparing a variety of trifluoromethyl derivatives, including those of sulphur.[1] This paper describes its extension to selenium which with trifluoroiodomethane in the optimum temperature range (260—285°) yielded bistrifluoromethyl selenide, b. p. −2°, and diselenide, b. p. 73°, in a ratio of about 4 : 1. The amount of diselenide fell rapidly above 285°, since the back-reaction, $(CF_3)_2Se_2 + I_2 \longrightarrow 2CF_3I + 2Se$, is almost quantitative at 315°: the monoselenide reacts much less readily with iodine. By contrast the reaction of trifluoroiodomethane with sulphur gives mainly disulphide with small amounts of tri- and tetra-sulphides, but no monosulphide.[1] Methyl iodide also reacts with selenium [2] but the product is trimethylselenonium iodide, which has no trifluoromethyl analogue.

Bistrifluoromethyl selenide resembled its sulphur analogue in being resistant to hydrolysis by water or aqueous alkali. This fact was used to remove traces of the diselenide, which was readily attacked by alkali. The monoselenide was, however, decomposed by 20% alcoholic potassium hydroxide at 100°:

$$CF_3{\cdot}Se{\cdot}CF_3 \xrightarrow{OH^-} CHF_3,\ F^-,\ Se^{2-},\ CO_3^{2-}$$

Parallel information on the stability of alkyl and aryl selenides is incomplete, but dimethyl selenide is not attacked by aqueous alkali at ordinary temperatures although it deposits selenium when boiled with water.[3] Di-*n*-propyl selenide and dibenzyl selenide are also stable when boiled with a 5% solution of sodium hydroxide in aqueous alcohol.[4] Dilute mineral acids did not hydrolyse bistrifluoromethyl selenide, and it was unattacked by concentrated nitric acid, in contrast to dimethyl selenide, which is said [3] to be oxidised to a salt of the selenoxide, $Me_2Se(OH)NO_3$.

Mercuric chloride did not react with bistrifluoromethyl selenide, whereas dialkyl selenides readily form addition compounds. Bistrifluoromethyl selenide also failed to form a selenonium compound with methyl iodide. These differences arise from the presence of the highly electronegative trifluoromethyl group in the molecule and are also found with other groups which delocalise the lone pairs of electrons on the selenium. Thus, diphenyl selenide and ethyl iodide do not react,[5] and dimethylphenylselenonium

* Part XIII, *J.*, 1957, 3708.

† Presented at Amer. Chem. Soc. Meeting, Atlantic City, 1952, Abstracts, p. 14K.

[1] Brandt, Emeléus, and Haszeldine, *J.*, 1952, 2552 *et seq.*; Haszeldine and Kidd, *J.*, 1954, 4228 *et seq.*

[2] Scott, *Proc. Chem. Soc.*, 1904, **20**, 156.

[3] Jackson, *Annalen*, 1875, **179**, 1.

[4] Painter, Franke, and Gortner, *J. Org. Chem.*, 1940, **5**, 579.

[5] Leicester and Bergstrom, *J. Amer. Chem. Soc.*, 1929, **51**, 3587.

XUM

iodide is formed only in very poor yield from methyl phenyl selenide and methyl iodide.[6] The triarylselenonium halides also dissociate readily at their melting points.[5,7]

Chlorine and dialkyl selenides readily form dihalides of the type R_2SeX_2, which are stable when X = Cl or Br but unstable when X = I; diaryl selenides behave similarly on direct halogenation and no compounds of the types RSeX and $RSeX_3$ are formed, although mixed alkyl aryl selenides tend to lose alkyl halide when heated and form arylselenium monohalides.[8] Bistrifluoromethyl selenide reacted slowly with chlorine at room temperature, and rapidly at 150°, to form an approximately equimolar mixture of selenium tetrachloride and trifluoromethylselenium trichloride, together with chlorotrifluoromethane. Photochemical reaction with light of wavelength >3000 Å gave trifluoromethylselenium trichloride almost quantitatively. There was no indication of the formation of a stable dichloride, $(CF_3)_2SeCl_2$.

Bistrifluoromethyl diselenide was distinctly more reactive than the monoselenide. It was rapidly decomposed by water at 100° with deposition of selenium and, with aqueous alkali, gave fluoride, carbonate, polyselenide ion, and selenium, even below 0°. No fluoroform was produced and the intermediates were presumably the selenol, $CF_3{\cdot}SeH$, and trifluoromethylselenenic acid, $CF_3{\cdot}SeOH$, both of which immediately reacted further as in the case of their sulphur analogues.[9] The diselenide was also hydrolysed by 3N-hydrochloric acid at 100°. Hydrolysis thus occurs more readily than with bistrifluoromethyl disulphide. There is little information on the ease of hydrolysis of alkyl and aryl diselenides, though the latter must be fairly resistant since their preparation can involve strongly alkaline media. Dipropyl and dibenzyl diselenide are decomposed by boiling aqueous-ethanolic 5% sodium hydroxide.[4]

Bistrifluoromethyl diselenide formed no addition compound with mercuric chloride or iodide. Aryl diselenides form compounds such as $(C_6H_5)_2Se_2{,}2HgCl_2$,[10] whereas with alkyl diselenides the Se–Se bond is cleaved, affording products such as $CH_3{\cdot}Se{\cdot}HgCl$.[11]

Chlorine reacted with bistrifluoromethyl diselenide, even at −50°, converting it into the trichloride, $CF_3{\cdot}SeCl_3$, which formed almost colourless crystals. By use of a limited amount of chlorine, trifluoromethylselenenyl chloride, $CF_3{\cdot}SeCl$, was obtained. This was a cherry-red liquid (b. p. 31°) which was also obtained by dissolving the solid trichloride in the diselenide. Bromine and bistrifluoromethyl diselenide were miscible and did not react at room temperature, but at 150° selenium tetrabromide and bromotrifluoromethane were formed. At 75°, however, trifluoromethylselenenyl bromide, $CF_3{\cdot}SeBr$, resulted, and there was no tribromide in the product. Iodine, which was readily soluble in bistrifluoromethyl diselenide, reacted with it, to give trifluoroiodomethane only at temperatures in excess of 160°. Trichloromethylselenenyl chloride, $CCl_3{\cdot}SeCl$, is known, but in attempts to effect reaction with chlorine to give $CCl_3{\cdot}SeCl_3$, fission of the C–Se bond occurred. Arylselenium compounds analogous to the trifluoromethyl compounds are known, however, *e.g.*, PhSeBr, $PhSeBr_3$.[12]

Concentrated nitric acid with bistrifluoromethyl diselenide gave trifluoromethylseleninic acid, $CF_3{\cdot}SeO{\cdot}OH$ (m. p. 118·5—119°), in high yield. This was stable and nondeliquescent but volatile in water vapour. It was also obtained by exposure of trifluoromethylselenium trichloride to moist air. It is a strong acid, and the increase in strength compared with that for the alkylseleninic acids (*e.g.*, $CH_3{\cdot}SeO_2H$: K $6{\cdot}4 \times 10^{-6}$; $C_2H_5{\cdot}SeO_2H$: K $5{\cdot}3 \times 10^{-6}$ at 25°)[13] parallels the effect noted earlier with the acids of

[6] Baker and Moffitt, *J.*, 1930, 1722.
[7] Leicester and Bergstrom, *J. Amer. Chem. Soc.*, 1931, **53**, 4428.
[8] Jackson, *Ber.*, 1875, **8**, 109; Behaghel and Hofmann, *Ber.*, 1939, **72**, 697; Edwards, Gaythwaite, Kenyon, and Phillips, *J.*, 1928, 2293.
[9] Haszeldine and Kidd, *J.*, 1955, 2901.
[10] Bradt and Green, *J. Org. Chem.*, 1937, **1**, 540.
[11] Bird and Challenger, *J.*, 1942, 570.
[12] Behaghel and Seibert, *Ber.*, 1932, **65**, 812.
[13] Backer and van Dam, *Rec. Trav. chim.*, 1930, **49**, 479.

XUM

phosphorus, arsenic, and antimony. The hydrolysis of trifluoromethylselenium trichloride is analogous to that of alkyl- and aryl-selenium trihalides.[11,14]

Trifluoromethylselenenyl chloride was hydrolysed readily by water with formation of the diselenide in amounts which agree with the following overall equation:

$$3CF_3{\cdot}SeCl + 2H_2O \longrightarrow CF_3{\cdot}SeO_2H + CF_3{\cdot}Se_2{\cdot}CF_3 + 3HCl$$

The seleninic acid produced was not recovered quantitatively because of losses due to its volatility with water vapour. Hydrolysis of trifluoromethylselenenyl chloride with 25% sodium hydroxide solution occurred readily and gave approximately one-third of the fluorine as fluoroform and two-thirds as fluoride. This implies that the initial reaction proceeds according to the equation for the aqueous hydrolysis; sodium trifluoromethylseleninate is decomposed by alkali with liberation of a mol. of fluoroform, and the diselenide decomposes immediately with alkali, liberating six fluoride ions per molecule.

Attempts to oxidise trifluoromethylseleninic acid to the seleninic acid, $CF_3{\cdot}SeO_3H$, were unsuccessful with nitric acid or 100-volume hydrogen peroxide. Hydrolysis of the trifluoromethylselenium trichloride with 100-volume hydrogen peroxide also gave only the seleninic acid in spite of the liberation of free chlorine, which is known to be effective for the oxidation of phenylseleninic acid to phenylselenonic acid,[15] although tolylselenonic acids are said to liberate chlorine from hydrochloric acid.[16]

Trifluoromethylselenenyl chloride reacted rapidly and quantitatively with mercury, forming bis(trifluoromethylseleno)mercury, $Hg(Se{\cdot}CF_3)_2$, which was separated by sublimation. The chlorine atom was also replaced by cyanide on reaction with silver cyanide; trifluoromethyl selenocyanate so obtained was stable to water but was decomposed by 20% aqueous alkali with quantitative formation of fluoride ion. Bistrifluoromethyl diselenide formed the mercurial $Hg(Se{\cdot}CF_3)_2$ when merely shaken with mercury, indicating a weak Se–Se bond. Formation of the sulphur analogue $Hg(S{\cdot}CF_3)_2$ requires much more vigorous conditions involving photochemical cleavage of the S–S bond of bistrifluoromethyl disulphide. Photochemical reaction of bistrifluoromethyl diselenide with mercury expedites formation of the mercurial, with bistrifluoromethyl selenide and selenium as by-products. Bis(trifluoromethylseleno)mercury formed pale yellow crystals, m. p. 51°, which sublimed *in vacuo* and were readily soluble in water or organic solvents. The compound $Hg(Se{\cdot}C_2H_5)_2$ has been prepared from ethyl hydrogen selenide, $C_2H_5{\cdot}SeH$, and mercuric oxide, but its properties have not been fully described; the methyl analogue is reported to be also formed in the reaction of methyl hydrogen selenide with mercuric cyanide.[17]

Chlorine reacted rapidly and quantitatively with the mercurial, thus:

$$Hg(Se{\cdot}CF_3)_2 + 2Cl_2 = HgCl_2 + 2CF_3{\cdot}SeCl$$

and there was no evidence for the formation of the compound $CF_3{\cdot}Se{\cdot}HgCl$ as intermediate when a deficit of chlorine was used. The sulphur analogue $CF_3{\cdot}S{\cdot}HgCl$ is produced, together with trifluoromethylsulphenyl chloride, by chlorination of bis(trifluoromethylthio)mercury.[18] Bromine and bis(trifluoromethylseleno)mercury similarly gave trifluoromethylselenenyl bromide. Reaction of bis(trifluoromethylthio)mercury with hydrogen chloride gives an almost quantitative yield of the thiol, $CF_3{\cdot}SH$,[18] but the corresponding reaction with the selenium analogue was more complicated. Reaction was negligible at room temperature, but at 50—100° low yields of the analogue, $CF_3{\cdot}SeH$, were obtained, together with the diselenide, $(CF_3)_2Se_2$, and a small amount of a high-boiling material which may have contained polyselenides. The solid residue also contained, in addition to unchanged starting material and mercuric chloride, the white crystalline intermediate

[14] Douglass, Brower, and Martin, *J. Amer. Chem. Soc.*, 1952, **74**, 5770.
[15] Stoecker and Krafft, *Ber.*, 1906, **39**, 2197; *J.*, 1906, **90**, 568.
[16] Doughty and Elder, 8th Intern. Congr. Appl. Chem., 1912, Vol. VI, p. 93.
[17] Siemens, *Annalen*, 1847, **61**, 360; Baroni, *Atti Accad. Lincei*, 1930, **12**, 234.
[18] Haszeldine and Kidd, *J.*, 1953, 3219.

XUM

CF_3·Se·HgCl, which was synthesised separately by reaction of equimolar quantities of bis(trifluoromethylseleno)mercury with mercuric chloride in ether.

Trifluoromethyl hydrogen sulphide, CF_3·SeH, is colourless and boils at −14·5°, which is 2° lower than the methyl analogue CH_3·SeH.[17] Alkaline hydrolysis rapidly gave all the fluorine as fluoride, together with carbonate, selenium, and alkali selenide or polyselenide.

The trifluoromethyl derivatives of selenium are thus characterised by (*a*) greater reactivity than the corresponding sulphur compounds, attributed to weaker C–Se and Se–Se bonds, (*b*) an ability to form quadrivalent selenium compounds involving halogen, *e.g.*, CF_3·$SeCl_3$, not readily formed by the corresponding sulphur compounds, and (*c*) formation of the seleninic acid, CF_3·SeO_2H, as the most stable oxy-acid, in contrast to the sulphonic acid CF_3·SO_3H. These trends are, in general, in accord with those observed with other derivatives of selenium and sulphur.

Experimental

Reaction of Selenium with Trifluoroiodomethane.—Experiments to determine optimum reaction conditions were made in Carius tubes (70—80 ml.) charged with about 5 g. of trifluoroiodomethane and 10 g. of roughly powdered selenium. A steel pressure-bottle (450 ml.), charged *in vacuo* with 100—150 g. of dried selenium and up to 70 g. of trifluoroiodomethane and rotated horizontally in a molten salt bath, was used in later experiments. Over sixty preparative runs were thus made. The optimum temperature range was 260—285°. Reaction was negligible at 240° while above 280° yields decreased rapidly and hexafluoroethane was formed. Under optimum conditions yields, based on trifluoroiodomethane used, were: $(CF_3)_2Se_2$, 10—15%; $(CF_3)_2Se$, 45—50%. Attempts to improve yields by adding iron powder to combine with free iodine showed little effect. The yield was increased when iodine was allowed to condense during the reaction in the unheated end of a Carius tube. Preliminary experiments showed that, in a specially designed reaction vessel, removal of iodine by reaction with mercury had a similar effect. Use of the rotating pressure vessel is most satisfactory for laboratory preparations.

Preliminary separation of the products by trap-to-trap distillation in a vacuum-apparatus of conventional type gave crude $(CF_3)_2Se_2$, b. p. 73°, crude $(CF_3)_2Se$, b. p. −2°, unchanged CF_3I, b. p. −22·5°, and more volatile products (SiF_4, COF_2, C_2F_6, etc.).

Small amounts of the diselenide were removed from the crude bistrifluoromethyl selenide by washing it with aqueous sodium hydroxide. Separation of the monoselenide from trifluoroiodomethane by trap-to-trap distillation proved difficult but distillation in a vacuum-jacketed low-temperature fractionation column gave pure *bistrifluoromethyl selenide*, b. p. −2° (Found: F, 52·9; Se, 36·2%; *M*, 217. C_2F_6Se requires F, 52·6: Se, 36·4%; *M*, 217).

Bistrifluoromethyl diselenide, b. p. 72·5—73·5°, was purified by column distillation (Found: F, 38·4; Se, 53·2%; *M*, 296. $C_2F_6Se_2$ requires F, 38·5; Se, 53·4%; *M*, 296). The residue from the distillation of the diselenide had a molecular weight of 309—315, indicating the presence of the triselenide, CF_3·Se_3·CF_3.

Reactions of Bistrifluoromethyl Selenide.—(a) *With alkali.* Bistrifluoromethyl selenide (0·483 g.) was unchanged after being sealed with 25% aqueous sodium hydroxide (4 ml.) and heated at 90—95° for 24 hr.

Bistrifluoromethyl selenide (1·018 g.) was heated in a Carius tube with potassium hydroxide (2·5 g.) and methanol (10 ml.) at 95—100° for 19 hr. The tube was etched and 0·347 g. (65%) of fluoride was found in the hydrolysate. Fluoroform (0·221 g., 35%) was evolved.

(b) *With nitric acid.* Bistrifluoromethyl selenide (0·5 g.) did not react when sealed with concentrated nitric acid (1·5 ml.) and shaken for 4·5 hr. at 80—90°.

(c) *With methyl iodide and mercuric chloride.* Bistrifluoromethyl selenide (0·78 g.) and methyl iodide (0·55 g.) failed to react in a sealed tube at 135° in 4 hr.

There was no reaction between the monoselenide (0·468 g.) and mercuric chloride (1·84 g.) at room temperature or after 16 hr. at 130°.

(d) *With chlorine.* Bistrifluoromethyl selenide (5·0 g.) and chlorine (1·64 g.) when sealed together in a Carius tube at 20° (24 hr.) deposited small white crystals. The volatile products were removed, the tube was filled with dry nitrogen, and the end containing the solid products was heated in an oil-bath. An almost colourless solid sublimed rapidly at 100°. The pale

yellow solid residue (0·99 g.) dissolved in 15% sodium hydroxide solution without gas evolution (Found: Cl, 64·0. Calc. for Cl_4Se: Cl, 64·3%). The sublimate (1·19 g.) was *trifluoromethylselenium trichloride* (Found: Cl, 42·3. CCl_3F_3Se requires Cl, 41·9%), m. p. 88—89° (sealed tube), sublimes at *ca.* 85°. Fractionation of the more volatile products gave chlorotrifluoromethane (1·50 g.) (Found: *M*, 102·5. Calc. for $CClF_3$: *M*, 104·5) and unchanged monoselenide (2·91 g.) (Found: *M*, 213. Calc. for C_2F_6Se: *M*, 216), identified by their infrared spectra. Reaction of bistrifluoromethyl selenide and chlorine at 150° is complete in 4 hr., to give an approximately equimolar mixture of selenium tetrachloride and trifluoromethylselenium trichloride.

In a second experiment bistrifluoromethyl selenide (1·54 g.) and chlorine (1·026 g.), sealed in a quartz tube, were shaken and exposed to unfiltered radiation from a Hanovia lamp with an S-250 U-type arc at 5 cm. Removal of volatile material gave only residual white selenium tetrachloride (Found: Cl, 66·3. Calc. for Cl_4Se: Cl, 64·3%), subliming at 193—200°.

In a third experiment the monoselenide (1·75 g.) and chlorine (0·341 g.) were irradiated as before for 16 hr. in a Pyrex tube. In the early stages the tube contained a red liquid and vapour (CF_3·SeCl, see below) which gradually changed to a red-brown solid mixed with white fern-like crystals. The readily volatile products were removed, washed with 10% sodium hydroxide solution, and fractionated to give chlorotrifluoromethane (0·197 g.) (Found: *M*, 103. Calc. for $CClF_3$: *M*, 104·5) and bistrifluoromethyl selenide (1·25 g.) (Found: *M*, 211. Calc. for C_2F_6Se: *M*, 217). The solid residue (0·540 g.), which sublimed under dry nitrogen at 85—90° (Found: Cl, 41·3. CCl_3F_3Se requires Cl, 41·8%), was *trifluoromethylselenium trichloride* uncontaminated by selenium tetrachloride.

Reactions of Bistrifluoromethyl Diselenide.—(a) *With water, aqueous alkali, or aqueous acid.* The diselenide was immiscible with water and there was no sign of reaction on shaking them at 20° for 24 hr., even with acetone present to provide miscibility. Reaction with water occurred at 100° with deposition of selenium and etching of the tube. Reaction with aqueous alkali was rapid and complete, even below 0°, forming fluoride, polyselenide, and carbonate, but no fluoroform. This reaction was used in analysing the compound. The diselenide (0·62 g.) with 3N-hydrochloric acid at 100° for 22 hr. gave a grey-black crust of selenium and the tube was etched. The colourless gas evolved (0·21 g.) (Found: *M*, 47·5) was absorbed by 10% aqueous alkali with <1 ml. of residue and was probably carbon dioxide with a small proportion of hydrogen selenide. Complete hydrolysis of the diselenide would give 0·184 g. of carbon dioxide.

(b) *With mercuric chloride or iodide.* The diselenide [(*a*) 0·428 g., (*b*) 0·471 g.] was recovered unchanged after being heated at 200° (48 hr.) in a sealed tube with (*a*) mercuric chloride (0·975 g.) or (*b*) mercuric iodide (0·721 g.).

(c) *With chlorine.* Bistrifluoromethyl diselenide (1·106 g.) was sealed in a Carius tube with chlorine (0·378 g.). Reaction below room temperature gave a red liquid with suspended crystals. Readily volatile products were pumped off, to leave *trifluoromethylselenium trichloride* (Found: Cl 41·7; Se, 31·5. CCl_3F_3Se requires Cl, 41·8; Se, 31·1%), m. p. 88—89° after sublimation. Hydrolysis by aqueous alkali gave fluoroform (0·0406 g.) (Found: *M*, 73. Calc. for CHF_3: *M*, 70). The theoretical yield from the sample for analysis (0·178 g.) would be 0·049 g. if hydrolysis occurred according to the equation:

$$CF_3{\cdot}SeCl_3 + 5NaOH = 3NaCl + Na_2SeO_3 + CHF_3 + 2H_2O$$

The volatile red liquid was mainly trifluoromethylselenenyl chloride containing some diselenide (Found: Se, 44·5; Cl, 17·0. Calc. for $CClF_3Se$: Se, 43·1; Cl, 19·35%).

Bistrifluoromethyl diselenide (1·462 g.) with an excess of chlorine (1·794 g.) at room temperature rapidly gave a 97% yield of trifluoromethylselenium trichloride and only a trace of selenium tetrachloride. The volatile products were washed with aqueous alkali to remove chlorine and gave 8 ml. of a colourless gas (Found: *M*, 110. Calc. for $CClF_3$: *M*, 104·5).

In an experiment with a deficit of chlorine the diselenide (2·467 g.) and chlorine (0·725 g.) gave trifluoromethylselenium trichloride (0·625 g.) and a red liquid which was fractionated in a small column, to give *trifluoromethylselenenyl chloride* (1·760 g.) (Found: F, 31·3; Cl, 19·2; Se, 42·8%; *M*, 185. $CClF_3Se$ requires F, 31·1; Cl, 19·4; Se, 43·0%; *M*, 183·5), b. p. 31—31·5°. The residue solidified to pale yellow crystals (Found: Cl, 41·7. Calc. for CCl_2F_3Se: Cl, 41·8%).

Reactions of Trifluoromethylselenium Trichloride.—(a) *With bistrifluoromethyl diselenide.*

XUM

The diselenide (1·91 g.) and the trichloride (1·65 g.), mixed at room temperature, gave 3·33 g. of trifluoromethylselenenyl chloride (b. p. 30—31·5°).

(b) *With water.* The trichloride (0·540 g.) was placed in one end of an almost horizontal Carius tube with about 0·5 ml. of water in the other; the tube was then partly evacuated and sealed. In 8 hr. the crystals had deliquesced completely. Hydrochloric acid and water were pumped off (Found: 0·229 g. of HCl, 99% of that for complete hydrolysis of the trichloride). The solid was volatile with water vapour.

Trifluoromethylselenium trichloride (0·110 g.) when exposed to moist air on a watch-glass gave in 36 hr. chloride-free water-soluble white crystals (0·0313 g.) which were unchanged in weight on a further 10 hours' exposure to air or on being dried over phosphoric oxide. The *trifluoromethylseleninic acid* (Found: Se, 43·8; F, 31·3. CHO_2F_3Se requires Se, 43·7; F, 31·5%), m. p. 118·5—119°, rapid decomp. at 205°, was decomposed by sodium–potassium alloy for analysis. The yield in duplicate experiments with this procedure was about 40%, because of volatility of the acid with water vapour. The titration curve in aqueous solution was typical of a strong monobasic acid (Found: equiv., 183. $CF_3{\cdot}SeO{\cdot}OH$ requires equiv., 183).

The acid was also prepared by shaking bistrifluoromethyl diselenide (1·053 g.) with concentrated nitric acid (5 ml.) in a Carius tube (24°, 12 hr.). Products volatile at −15° were pumped off and the solid residue was heated *in vacuo* to 35—40° to remove unchanged nitric acid (*ca.* 0·5 ml.). The residue was kept in an evacuated desiccator over phosphoric oxide for 9 days to give trifluoromethylseleninic acid (mixed m. p. 117·9—118·2°) with an infrared spectrum identical with that of the hydrolysis product from trifluoromethylselenium trichloride. The white silver salt of the acid was moderately soluble in water.

Reaction of Trifluoromethylselenenyl Chloride.—(a) *With water.* Trifluoromethylselenenyl chloride (0·488 g.) was sealed in an evacuated Carius tube with 1 ml. of water frozen at the bottom. When the monochloride melted and came into contact with the ice there was a mild reaction and drops of a pale yellow liquid were formed. The volatile products were removed, leaving a white crystalline residue, identified by mixed m. p. as trifluoromethylseleninic acid. The yellow oil which separated from the water layer in the volatile fraction was bistrifluoromethyl diselenide (0·249 g.), b. p. 72—73° (Found: F, 38·1. Calc. for $C_2F_6Se_2$: F, 38·5%). The theoretical yield of diselenide for the reaction, $3CF_3{\cdot}SeCl + 2H_2O = (CF_3)_2Se_2 + CF_3{\cdot}SeO{\cdot}OH + 3HCl$, was 0·262 g. The presence of selenium in the aqueous layer was confirmed by reduction with hydrazine.

(b) *With aqueous alkali.* Trifluoromethylselenenyl chloride (0·241 g.) with 20% aqueous sodium hydroxide (3 ml.) at 100° for 4 hr. gave fluoroform (0·029 g., 32%), chloride (Found: Cl, 19·1. Calc. for $CClF_3Se$: Cl, 19·4%), and fluoride (0·0498 g., 68%).

(c) *With silver cyanide.* Trifluoromethylselenenyl chloride (3·02 g.) and dried silver cyanide (10 g.) in a sealed tube below 0° gave smoothly *trifluoromethyl selenocyanate* (2·86 g.), b. p. 84°/758 mm. It was decomposed for analysis by sodium–potassium alloy (Found: Se, 45·2; F, 32·5%; *M*, 175. C_2F_3NSe requires Se, 45·4; F, 32·8%; *M*, 174).

Reaction of Bistrifluoromethyl Diselenide with Bromine.—Bistrifluoromethyl diselenide (0·806 g.) and dry bromine (1·690 g.) were heated in a sealed tube at 100—155° for 20 hr. The readily volatile products were removed, leaving a red-brown solid (1·27 g.) (Found: Br, 80·0; Se, 19·6. Calc. for Br_4Se: Br, 80·2; Se, 19·8%). The volatile material gave selenium tetrabromide (*ca.* 0·02 g.) and bromotrifluoromethane (0·499 g.) contaminated with unchanged diselenide.

Under milder conditions (70—75°, 12 hr.) bistrifluoromethyl diselenide (6·86 g.) and bromine (7·4 g.) gave, after fractionation, *trifluoromethylselenenyl bromide* (8·3 g.), b. p. 53·5—54·3° (Found: Br, 35·4; Se, 34·2%; *M*, 229. $CBrF_3Se$ requires Br, 35·1; Se, 34·6%; *M*, 228). Attempts to prepare trifluoromethylselenium tribromide by varying the reaction conditions and the proportion of bromine were unsuccessful.

When the monobromide (1·32 g.) was shaken with water (5 ml.) bistrifluoromethyl diselenide (0·548 g.), b. p. 72—72·7°, was formed. This is a 96% yield for the reaction, $3CF_3{\cdot}SeBr + 2H_2O = (CF_3)_2Se_2 + CF_3{\cdot}SeO_2H + 3HBr$.

Trifluoromethylselenenyl bromide (0·564 g.) was sealed with mercury (2 ml.) and shaken for a few minutes at room temperature. The product was bistrifluoromethyl diselenide (0·358 g.) (Found: *M*, 293. Calc. for $C_2F_6Se_2$: *M*, 296).

Reaction of Bistrifluoromethyl Diselenide with Iodine.—Bistrifluoromethyl diselenide (0·680 g.) was heated at 150—160° for 66 hr. with dried iodine (0·926 g.). Diselenide (0·666 g.) (Found:

XUM

M, 297) and iodine (0·910 g.) were recovered. The recovered material, reheated at 315—320° for 48 hr., gave trifluoroiodomethane (0·520 g.) (Found: *M*, 198. Calc. for CIF_3: *M*, 196).

Reaction of Bistrifluoromethyl Diselenide with Mercury.—The diselenide (0·618 g.) was sealed in a quartz Carius tube with mercury (2 ml.) and shaken (20 hr.) at 4 cm. from the mercury arc lamp. The volatile products were bistrifluoromethyl diselenide (0·175 g.) (Found: *M*, 294. Calc. for $C_2F_6Se_2$: *M*, 296) and 0·035 g. of a gas (Found: *M*, 223) which was probably bistrifluoromethyl selenide (*M*, 217). The residue in the tube was extracted with ether, and the product obtained on evaporation was sublimed in a vacuum at 50°, to give *bis(trifluoromethylseleno)mercury* (0·395 g.) as yellow needles with an unpleasant pungent odour. It was decomposed for analysis by sodium–potassium alloy at 525° (Found: F, 22·8; Se, 31·5. $C_2F_6Se_2Hg$ requires F, 23·0; Se, 31·8%). The resublimed crystals melted sharply at 51°. A yield of 96% was obtained by using more efficient shaking and subliming the product directly instead of extracting it with ether. A further quantity of this compound was recovered from the residues left from the mercury treatment of crude bistrifluoromethyl diselenide fractions from the selenium–trifluoroiodomethane reaction.

Reaction of Bis(trifluoromethylseleno)mercury.—(a) *With chlorine.* Bis(trifluoromethylseleno)mercury (2·60 g.) was sealed in a Carius tube with chlorine (0·735 g.). Reaction was rapid below room temperature. The volatile product after 20 hr. at 16° was trifluoromethylselenenyl chloride (1·910 g.) (Found: F, 30·9; Cl, 19·2; Se, 42·8. Calc. for $CClF_3Se$: F, 31·1; Cl, 19·4; Se, 43·0%).

(b) *With bromine.* Bromine (4·02 g.) and bis(trifluoromethylseleno)mercury (6·25 g.) were shaken in a Carius tube at 25° for 4 hr. The volatile product was trifluoromethylselenenyl bromide, b. p. 53·7—54·4° (4·82 g.). The residue in the tube (4·38 g.; m. p. 233°) was mercuric bromide.

(c) *With hydrogen chloride.* In a typical experiment the mercurial (9·0 g.) and anhydrous hydrogen chloride (1·32 g.) were heated in a Carius tube at 95—103° for 100 min. Fractionation of the product gave 0·742 g. of material, condensed at −140° (Found: *M*, 148. CHF_3Se requires *M*, 149). Refractionation gave *trifluoromethyl hydrogen selenide* (Found: F, 37·9; Se, 52·5. CF_3·SeH requires F, 38·3; Se, 53·0%), b. p. −14·5°/758 mm., unattacked by dry air at 20° but rapidly decomposed by water.

(d) *With mercuric chloride.* Bis(trifluoromethylseleno)mercury (0·212 g.) and mercuric chloride (0·116 g.) were dissolved in ether, which was then evaporated. The solid, which differed in appearance from the mercurial and melted to a clear liquid at 185—190°, was CF_3·Se·HgCl.

Analytical Procedures.—For analysis, certain of the more stable compounds [*e.g.*, $(CF_3)_2Se$] were heated at 500—550° with an excess of sodium or sodium–potassium alloy in a Carius tube. Unchanged alkali metal was destroyed with a few ml. of methanol. The contents of the tube were transferred to a Willard and Winter fluoride distillation apparatus and warmed with 10 ml. of 100-vol. hydrogen peroxide to oxidise inorganic selenide and polyselenides, and, in part, selenium to selenite. The contents of the flask were concentrated to 20 ml., concentrated sulphuric acid (40 ml.) was added, and the fluoride determined in the usual way. The residue in the distillation flask was transferred to a 500 ml. Erlenmeyer flask, the distillation flask being rinsed with hot nitric acid (5 ml.) to dissolve residual grey selenium. The liquid was evaporated to fumes of sulphuric acid, nitric acid (5 ml.) was added, and the evaporation repeated. The cooled sulphuric acid solution was diluted to 100 ml. and filtered and the filtrate digested for 1 hr. at 80—90° with concentrated hydrochloric acid (20 ml.) to reduce selenate to selenite. To the cooled solution was added slowly hydrazine hydrate (6—7 ml.) in water (20 ml.). After digestion on a steam bath for 2 hr. to convert selenium into the grey form, the latter was filtered off, dried at 100—120°, and weighed.

Compounds decomposed by alkaline hydrolysis [*e.g.*, $(CF_3)_2Se_2$] were treated with hydrogen peroxide after hydrolysis and the above procedure for determining fluorine and selenium was repeated.

Halogens were usually determined as silver halide on a separate sample, contamination by sparingly soluble silver selenite or silver trifluoromethyl seleninate being avoided by washing with hot water or warm dilute nitric acid.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, February 11th*, 1958.]

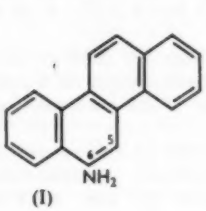
XUM

600. *Carcinogenic Nitrogen Compounds. Part XXV.* Steric Hindrance to Cyclisation of 6-Aminochrysene and its Derivatives.*

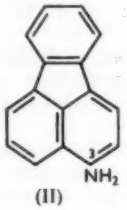
By G. C. Barrett and Ng. Ph. Buu-Hoï.

6-Aminochrysene failed to undergo further cyclisation in three standard reactions, probably on account of steric hindrance at position 5. Another anomaly was that 4′-hydroxy-6′-methylpyridino(2′ : 3′-6 : 5)chrysene, on zinc dust distillation, gave not the expected methylchrysenopyridine, but the corresponding compound with an oxygen bridge in the 4 : 4′-position. The less sterically hindered 3-aminofluoranthene gave an isatin derivative normally.

In view of the antitumour and leukopænia-producing effects of 6-aminochrysene [1] (I), we have investigated some properties of this amine and prepared some substitution products for biological examination. The present work records unsuccessful attempts to cause cyclisation at position 5.



(I)



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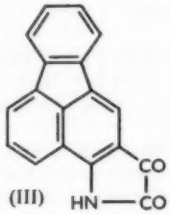

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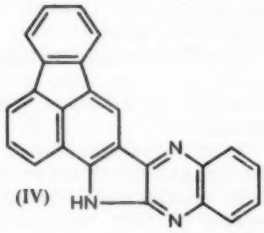
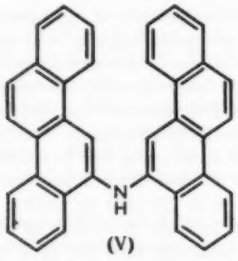


(IV)

6-Aminochrysene and diethyl mesoxalonate, under the conditions of the Martinet isatin synthesis,[2] failed to give the expected isatin derivative, although another tetracyclic arylamine, 3-aminofluoranthene (II), readily gave the dioxo-compound (III). With *o*-phenylenediamine, the last compound gave the heptacyclic compound (IV). Another failure was encountered in an attempt to synthesise phenarsazines by the Wieland–Rheinheimer reaction [3] of arsenic trichloride with di-6-chrysenylamine (V) and 6-2′-



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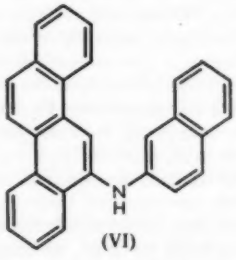


(VI)

naphthylaminochrysene (VI). Both these arylamines were obtained when 6-aminochrysene was condensed with β-naphthol in the presence of iodine, under the conditions of the Knoevenagel reaction,[4] even when β-naphthol was used in great excess. The analogous

* Part XXIV, *J.*, 1958, 738.

[1] Rudali, Buu-Hoï, and Lacassagne, *Compt. rend.*, 1953, **236**, 2020; Rudali and Buu-Hoï, *Le Sang*, 1955, **10**, 28.

[2] Martinet, *Ann. Chim.*, 1919, **11**, 15; Buu-Hoï and Hiong-Ki-Wei, *Rev. sci.*, 1944, **82**, 168, 306, 370.

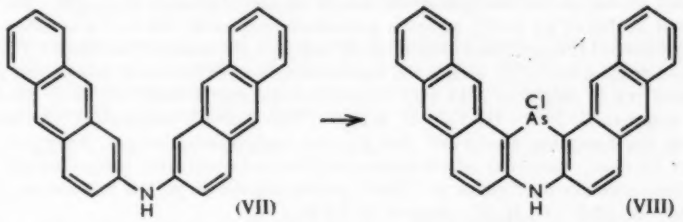
[3] Wieland and Rheinheimer, *Annalen*, 1921, **423**, 1; Burton and Gibson, *J.*, 1926, 2243; Buu-Hoï *et al.*, *Rev. sci.*, 1944, **82**, 453; 1945, **83**, 41.

[4] Knoevenagel, *J. prakt. Chem.*, 1914, **89**, 17; Buu-Hoï, *J.*, 1952, 4346.

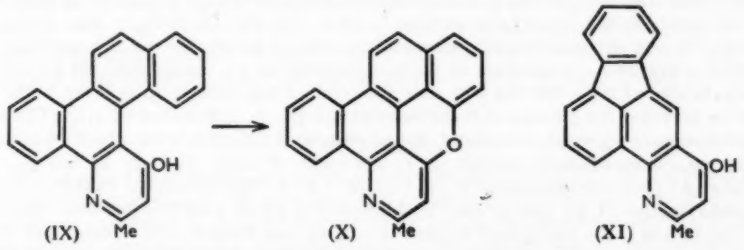
dichrysenylamine was also obtained when α-naphthol was used in place of β-naphthol. In contrast, di-2-anthrylamine (VII) gave 10-chloro-5 : 10-dihydrodinaphtho[2′ : 3′-1 : 2]-[2″ : 3″-8 : 9]phenarsazine (VIII) rapidly and in good yield.

The above failures are assumed to be caused by steric hindrance at position 5, which is seen when the formulæ (V) and (VI) are contrasted with (VII). The last amine, but not di-6-chrysenylamine, also gives a phenothiazine derivative on treatment with sulphur.

6-Aminochrysene did not react with ethyl acetoacetate in the presence of piperidine at room temperature, although 1-aminopyrene gives the imino-derivative in these conditions.[5] A more drastic procedure, use of boiling ethyl acetoacetate, resulted in direct



condensation [6] to 4-hydroxy-6-methylchryseno(6′ : 5′-2 : 3)pyridine (IX). A further anomaly was observed when the last compound was distilled with zinc dust, the oxygen-bridged compound (X) being obtained instead of the expected oxygen-free compound. A similar failure to eliminate an oxygen atom was experienced in the 1 : 2-benzanthracene series by Rădulescu and Bărbulescu [7] and could be explained by the high temperature of the reaction and the dehydrogenating action of zinc.



The direct Conrad–Limpach cyclisation, applied to 3-aminofluoranthene, readily gave the fluoranthenopyridine (XI); condensation of the same amine with acetonylacetone [8] yielded 3-(2 : 5-dimethyl-1-pyrryl)fluoranthene. Both the amines (I) and (II) gave monoanils with acetylacetone in excellent yields.

Experimental

Preparation of Intermediates.—6-Aminochrysene was prepared by reduction of 6-nitrochrysene,[9] and 3-aminofluoranthene, b. p. 280—290°/40 mm., by reduction of 3-nitrofluoranthene with powdered tin and hydrochloric acid; nitration of fluoranthene was effected at 75—80° in acetic acid.[10] 2-Anthrylamine was prepared by reduction of 2-aminoanthraquinone.[11]

6-(1-*Methyl*-3-*oxobutylimino*)*chrysene.*—A solution of 6-aminochrysene (10 g.) in acetylacetone (25 g.) was refluxed for 40 hr., the excess of acetylacetone was distilled off, and the

[5] Weizman and Bograchov, *J.*, 1942, 377.
[6] Conrad and Limpach, *Ber.*, 1891, **24**, 2990.
[7] Rădulescu and Bărbulescu, *Bull. Soc. chim. România*, 1939, **1**, III, 7; *Chem. Abs.*, 1943, **37**, 4070.
[8] Cf. Buu-Hoï, *J.*, 1949, 2882.
[9] Newman and Cathcart, *J. Org. Chem.*, 1940, **5**, 618.
[10] Garascia, Fries, and Ching, *ibid.*, 1952, **17**, 227.
[11] Ruggli and Henze, *Helv. Chim. Acta*, 1930, **13**, 409; Bollert, *Ber.*, 1883, **16**, 1635.

XUM

solid formed on cooling was collected, washed with acetone, and recrystallised from that solvent; the *anil* formed beige prisms (10·2 g.), m. p. 165° (Found: C, 85·0; H, 5·8; O, 5·1. $C_{22}H_{19}ON$ requires C, 84·9; H, 5·9; O, 4·9%).

3-(1-*Methyl*-3-*oxobutylimino*)*fluoranthene*.—A solution of 3-aminofluoranthene (2·3 g.) in acetonylacetone (10 g.) was treated as above, giving the *anil*, which crystallised as large yellow prisms (1·8 g.), m. p. 152°, from benzene (Found: C, 84·5; H, 5·8; N, 4·8. $C_{21}H_{17}ON$ requires C, 84·3; H, 5·7; N, 4·7%).

4 : 5-*Dihydro*-4 : 5-*dioxofluoroantheno*(3′ : 2′-2 : 3)*pyrrole* (III).—Diethyl mesoxalonate (2 g.) was refluxed with 3-aminofluoranthene (1 g.) in acetic acid (20 c.c.) for 1 hr.; the solution was concentrated *in vacuo*, the residue diluted with water, and the solid obtained was recrystallised from ethanol, giving an intermediate ester, as orange-tinged prisms, m. p. 229—231° (decomp.). A suspension of this (1 g.) in 4% aqueous potassium hydroxide (50 c.c.) was refluxed for 1 hr., and air was bubbled through the solution which was then filtered and acidified. The precipitate recrystallised from acetic acid, giving the *isatin derivative*, violet-black prisms (0·7 g.), decomp. >320°, dissolving in sulphuric acid with brown halochromy (Found: C, 79·4; H, 3·4; N, 5·1. $C_{18}H_9O_2N$ requires C, 79·7; H, 3·3; N, 5·2%). The derived *quinoxaline* (IV) was prepared by refluxing the foregoing compound (0·5 g.) and *o*-phenylenediamine (0·5 g.) in acetic acid (40 c.c.) for 15 min.; the solid which separated from solution after concentration crystallised from pyridine as yellow needles, m. p. >320°, giving a greenish-yellow halochromy in sulphuric acid (Found: N, 12·0. $C_{32}H_{19}N_3$ requires N, 12·2%).

Condensation of 6-*Aminochrysene*.—(a) *With* β-*naphthol*. A mixture of 6-aminochrysene (10 g.), β-naphthol (15 g.), and iodine (0·1 g.) was heated at 180—200° for 5 hr., steam being evolved. The product was poured into 10% aqueous sodium hydroxide (100 c.c.), and the insoluble portion was collected, washed with water, and treated with acetone. The acetone solution gave, on evaporation, 6-2′-*naphthylaminochrysene* (VI), crystallizing from benzene as greyish prisms (5 g.), m. p. 188° (Found: C, 90·7; H, 5·3; N, 3·8. $C_{28}H_{19}N$ requires C, 91·0; H, 5·2; N, 3·8%). The portion insoluble in acetone (4·2 g.) was recrystallised from benzene (blue fluorescent solution), giving *di*-6-*chrysenylamine* (V), yellowish prisms, m. p. 314° (Found: C, 91·8; H, 5·0; N, 2·8. $C_{36}H_{23}N$ requires C, 92·1; H, 4·9; N, 3·0%). The proportion of compound (VI) was not substantially enhanced by using a greater excess of β-naphthol.

(b) *With* α-*naphthol*. A mixture of 6-aminochrysene (5 g.), α-naphthol (20 g.) and iodine (0·1 g.) was heated at 200—230° for 3 hr., and the product was worked up as in (a). The portion insoluble in acetone (3·8 g.) was di-6-chrysenylamine (m. p. and mixed m. p.). The acetone-soluble portion gave a greyish compound, giving on recrystallisation from ethanol 6-1′-*naphthylaminochrysene*, cream-coloured needles, m. p. 208—209° (Found: C, 91·3; H, 5·5%).

10-*Chloro*-5 : 10-*dihydrodinaphtho*(2′ : 3′-1 : 2)(2″ : 3″-8 : 9)*phenarsazine* (VIII).—A solution of di-2-anthrylamine (1 g.) and arsenic trichloride (0·5 g.) in *o*-dichlorobenzene (10 c.c.) was refluxed for 30 min.; the precipitate formed on cooling was washed with ethanol and recrystallised from nitrobenzene, forming orange leaflets (0·7 g.), m. p. >340° (decomp. from 225°), giving a red halochromy in sulphuric acid (Found: C, 70·6; H, 3·8. $C_{28}H_{17}NAsCl$ requires C, 70·4; H, 3·6%).

Bernthsen Reaction with Di-2-*anthrylamine*.—This amine (0·5 g.; prepared from 2-anthrylamine [11]) was heated with sulphur (0·2 g.) and iodine (0·05 g.) at 200° until hydrogen sulphide ceased to be evolved; the product gave with sulphuric acid a deep violet colour characteristic of phenothiazine derivatives.[12] This reaction was negative with amine (V).

4-*Hydroxy*-6-*methylchryseno*(6′ : 5′-2 : 3)*pyridine* (IX).—A solution of 6-aminochrysene (5 g.) in ethyl acetoacetate (20 g.) was refluxed for 24 hr., then the excess of ethyl acetoacetate was distilled off, and the solid (3·5 g.) which separated on cooling was collected and recrystallised from nitrobenzene, giving colourless prisms, m. p. 360—362°, insoluble in ethanol and benzene (Found: C, 85·5; H, 5·1; N, 4·7. $C_{23}H_{15}ON$ requires C, 85·4; H, 4·9; N, 4·5%). An attempt to prepare the uncyclised intermediary imino-derivative by leaving for 4 days at room temperature a solution of 6-aminochrysene and ethyl acetoacetate in dioxan in the presence of piperidine resulted only in recovery of the amine.

2′-*Methyl*-1-*oxa*-3′-*aza*-2 : 3-4 : 5-*dibenzopyrene* (X).—An intimate mixture of the foregoing hydroxy-compound (2 g.) and zinc dust (20 g.) was dry distilled, and the solid distillate was recrystallised from ethanol–benzene, forming yellowish needles (0·7 g.), m. p. 210°, giving an intense yellow halochromy in sulphuric acid (Found: C, 85·9; H, 4·5. $C_{22}H_{13}ON$ requires

[12] Cf. Buu-Hoï, *Rev. sci.*, 1945, **83**, 170.

XUM

C, 86·0; H, 4·3%). The *picrate* formed deep yellow prisms, m. p. 207—208°, from xylene (Found: N, 10·1. $C_{28}H_{16}O_8N_4$ requires N, 10·4%).

4-Hydroxy-6-methylfluoranthenо(3′ : 2′-2 : 3)pyridine (XI).—A solution of 3-aminofluoranthene (1 g.) in ethyl acetoacetate (5 g.) was refluxed for 30 min.; the solid (1 g.) formed on cooling was collected, washed with acetone, and recrystallised from nitrobenzene, giving yellowish crystals, m. p. >360° (Found: C, 84·5; H, 4·6; N, 5·1. $C_{20}H_{13}ON$ requires C, 84·8; H, 4·6; N, 4·9%).

3-(2 : 5-Dimethyl-1-pyrryl)fluoranthene (XII).—A solution of 3-aminofluoranthene (3 g.) in acetonylacetone (5 g.) was refluxed for 30 min.; the solid (2·9 g.) obtained on cooling formed from acetic acid yellowish prisms, m. p. 169°, which darkened rapidly in air (Found: C, 89·1; H, 6·0; N, 4·7. $C_{22}H_{17}N$ requires C, 89·5; H, 5·8; N, 4·8%).

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601. *The Phosphates of Calcium. Part V.* Revision of the Earlier Space Diagram.*

By HENRY BASSETT.

The author's original diagram of the system CaO–P_2O_5–H_2O has been revised.

IT is fifty years since a space diagram of the system CaO–P_2O_5–H_2O was published.[1] Many data needed to represent the system exactly were then lacking, but most have since been gathered. A new diagram which is essentially true to scale can thus be constructed; it justifies the older one satisfactorily in spite of some minor modifications.

EXPERIMENTAL

Solubilities were determined by standard procedures in silica vessels. Equilibrium solutions were analysed gravimetrically, as were the solid calcium phosphates after being washed with water, acetone, and ether to remove mother liquor and solid phosphoric acids. The calcium phosphates were also examined microscopically. The composition of the solution decided between the three acids $H_6P_2O_9$, H_3PO_4, and $H_4P_2O_7$. When determining solubilities of the phosphoric acids themselves, not only were the equilibrium solutions analysed but also the crystals of acid after separation as completely as possible from the solution. This was as a check against the possible appearance of some new and unexpected acid, but it also gave a valuable distinction between points on the normal H_3PO_4 or $H_4P_2O_7$ curves and points on the retroflex portions of the $H_6P_2O_9$, H_3PO_4, and $H_4P_2O_7$ curves. Where the solution point was on a normal branch, the crystals would contain more P_2O_5 than the solution, but when it was on the retroflex parts of the curves the crystals would contain less P_2O_5 than the solution.

Phosphoric oxide was weighed as $Mg_2P_2O_7$ after preliminary separation with molybdate when necessary and calcium oxide as such after precipitation as oxalate. It was found essential to determine and allow for the small amount of phosphoric oxide present in the calcium oxide. In analyses of phosphoric acids all solutions were digested with a few c.c. of 2N-hydrochloric acid for at least ½ hr. before precipitation with magnesia mixture. Solids and solutions containing calcium oxide and over 60% of phosphoric acid were digested with nitric acid for some time before separation of phosphomolybdate precipitates.

The Boundaries of the Ice Field.—Freezing points of phosphoric acid solutions. A Beckmann thermometer and apparatus with a magnetic stirrer were used for the readings above −4° and

* Part IV, *J.*, 1917, **111**, 620.

[1] Bassett, *Z. anorg. Chem.*, 1908, **59**, 29.

XUM

a pentane thermometer which was also the stirrer for lower temperatures, obtained by means of solid carbon dioxide and acetone in a Dewar vessel. Several readings of the f. p. were taken in each case with decreasing amounts of supercooling; the accepted value was that obtained after least supercooling. Disturbance caused by heating of the coil of the electromagnet was overcome by winding fine lead tubing, through which cold water passed, over the coil. Solution for analysis was removed with a cooled pipette having a detachable filter bulb containing glass wool. Freezing points, with percentages of P_2O_5 in parentheses, were: $-0.389°$ (1·088), $-1.551°$ (4·690), $-3.315°$ (8·999), $-18.5°$ (25·86), $-30.0°$ (31·31), $-65.0°$ (41·01). By extrapolation the ice–$H_8P_2O_9$ cryohydric point is $-100.0°$ and 46·2% of P_2O_5.

The freezing-point curve of $H_8P_2O_9$ solutions was determined by Ross and Jones [2] who considered that the cryohydric point was at $-85°$ with 45·29% of P_2O_5. This is out of step with their other points on the solubility curve of $H_8P_2O_9$ but falls well on the freezing-point curve as shown in their paper and with the present results. It seems that Ross and Jones mistook the condition of extreme glassy viscosity prevailing at $-85°$ for a complete cryohydric crystallisation; their curves indicate $-100°$ as the most probable cryohydric temperature.

Solutions in equilibrium with ice and either calcium hydroxide or one or two of the calcium orthophosphates. These are described in Table 1

Solubilities of the Phosphoric Acids.—The complete solubility curve of $H_8P_2O_9$ agrees well with the results of Smith and Menzies [3] and of Ross and Jones.[2] A few points on both the normal and retroflex portions of the H_3PO_4 curve were obtained and agree well with Ross and

TABLE 1.

	Solution		Solid other than ice		
Temp.	CaO (%)	P_2O_5 (%)	CaO (%)	P_2O_5 (%)	Nature of solids other than ice
$-0.116°$	0·130	—	—	—	Coarse crystals of $Ca(OH)_2$ *
These three quintuple points would be very close together over a very small range of temperature and of CaO and P_2O_5 concentration [4]					$Ca(OH)_2$ and hydroxyapatite Hydroxyapatite and $Ca_2P_2O_8,xH_2O$ $Ca_2P_2O_8,xH_2O$ and $CaHPO_4,2H_2O$
-2.6	3·235	9·513	33·00	41·11	$CaHPO_4,2H_2O$
-5.5	5·251	16·25	32·62	41·20	"
-7.0	5·819	18·33	32·60	41·34	"
-7.5	6·10	19·62	29·91	43·74	$CaHPO_4,2H_2O$ and $CaH_4P_2O_8,H_2O$ *
-7.5	6·07	19·5	—	—	" " " †
-8.0	5·883	19·86	22·77	56·20	$CaH_4P_2O_8,H_2O$
-9.5	5·47	21·10	22·67	55·90	"
-20.0	3·638	28·95	22·67	56·09	"
-40.0	1·657	35·40	22·54	56·44	"
-100	trace	46·2	—	—	$CaH_4P_2O_8,H_2O$ and $H_8P_2O_9$ by extrapolation

* Bassett, *J.*, 1934, 1270. [4] Bassett, *J.*, 1917, **111**, 620.

* Direct determination of the quintuple point. The solid phase analysed was slightly moist.

† Quintuple point determined graphically as the point of intersection of the three curves: ice–$CaHPO_4,2H_2O$, ice–$CaH_4P_2O_8,H_2O$, and $CaHPO_4,2H_2O$–$CaH_4P_2O_8,H_2O$. The actual plots were of the three temperature–P_2O_5 and temperature–CaO curves corresponding to these.

Jones's figures, which only extended to the m. p. of H_3PO_4. Sufficient points were also determined to give an approximate indication of the $H_4P_2O_7$ solubility curve for which the only previous figure was the m. p.[4] but no great accuracy is claimed. Our cooling system gave very steady temperatures and mixtures reached equilibrium in 1—2 hr. The lowest temperature at which the solubility of $H_8P_2O_9$ could be determined was $-66°$ owing to the very high viscosity and it was difficult to obtain even 0·5 g. for analysis with the cooled pipette with filter bulb. The crystals could not be separated for examination until the temperature had risen to $-45°$. There was no indication that this changed the character of the crystals or that they were other than $H_8P_2O_9$.

Merck's syrupy phosphoric acid (64—65% of P_2O_5) was used for the solubility work on $H_8P_2O_9$, somewhat concentrated in platinum where necessary. Acids in the H_3PO_4 range were prepared by heating the syrupy acid in a platinum basin to temperatures not above 120° and acids in the $H_4P_2O_7$ range by heating the syrupy acid with redistilled $POCl_3$ to not above

[2] Ross and Jones, *J. Amer. Chem. Soc.*, 1925, **47**, 2165.
[3] Smith and Menzies, *J. Amer. Chem. Soc.*, 1909, **31**, 1183.
[4] Giran, *Compt. rend.*, 1908, **146**, 1270.

XUM

200°.[5] Acids so prepared had been kept for many months before being used for the solubility determinations.

Three experiments are included in Table 2, in two of which $CaH_4P_2O_8,H_2O$ and $H_3P_2O_9$

TABLE 2.

Temp.	Solution P_2O_5 (%)	Moist solid P_2O_5 (%)	Nature of solid phase
−100°	46·2	—	Ice and $H_3P_2O_9$ (by extrapn.)
−66	48·76	60·98	$H_3P_2O_9$
−53	49·10	65·06	,,
−35	51·26	62·42	,,
0	57·50	65·09	,,
0	57·20 [a]	—	$H_3P_2O_9$ and $CaH_4P_2O_8,H_2O$
3	57·60	63·50	$H_3P_2O_9$
14·7	60·32	65·13	,,
25	63·02 [b]	—	$H_3P_2O_9$ and $CaH_4P_2O_8,H_2O$
26·25	63·55	65·83	$H_3P_2O_9$
28·5	64·32	65·73	,,
29·35	66·35	66·35	M. p. of $H_3P_2O_9$ [c]
29	67·03	—	$H_3P_2O_9$
27·7	67·86	66·52	,,
25	68·44	67·24	,,
23·5	*68·64*	—	$H_3P_2O_9$ and H_3PO_4 [d]
37·6	*71·5*	—	H_3PO_4
42·35 [f]	*72·45*	*72·45*	—
35·75	74·05	—	H_3PO_4
25	77·06 [g]	76·49	,,
	77·02 [h]	—	,,
33·3	76·28	—	$H_4P_2O_7$
38	76·41	—	,,
41·5	76·64	77·00	,,
61 [i]	*79·77*	*79·77*	—
50·8	81·22	—	$H_4P_2O_7$
50	81·00	—	,,
47·1	81·11	—	,,

[a] +0·112% of CaO. [b] +0·204% of CaO. [c] Estimated from curve. [d] Eutectic; Ross and Jones (ref. 2). [e] + trace of CaO. [f] M. p. of H_3PO_4 (refs. 3 and 2). [g] After 4 weeks. [h] After 13 months. [i] M. p. of $H_4P_2O_7$ (ref. 4). Values in italics are from other sources.

were present as solid phases and in the other $CaH_4P_2O_8$ and H_3PO_4. The solubility of the calcium phosphate in the concentrated acids is so small as hardly to affect the P_2O_5 content of the solutions.

Other data used in constructing the space diagram. These are shown in Table 3. We also used the 25°, 40°, and 50·7° isothermals previously published [1] as well as the figures for the quintuple point at 152° (5·60% of CaO; 53·00% of P_2O_5).

TABLE 3.

Solution CaO (%)	Solution P_2O_5 (%)	Nature of solid phase
	0° Isothermal	
—	57·50	$H_3P_2O_9$
0·112	57·20	$H_3P_2O_9$ and $CaH_4P_2O_8,H_2O$
0·716	46·94	$CaH_4P_2O_8,H_2O$
2·859	35·40	,,
4·482	27·96	,,
6·008	20·55	$CaH_4P_2O_8,H_2O$ and $CaHPO_4,2H_2O$
4·822	15·47	$CaHPO_4,2H_2O$
2·23	6·365	,,
	25° Isothermal	
0·204	63·02	$H_3P_2O_9$ and $CaH_4P_2O_8,H_2O$
5·885	24·40	$CaH_4P_2O_8,H_2O$ and $CaHPO_4$ (stable)
6·58	22·62	$CaH_4P_2O_8,H_2O$ and $CaHPO_4,2H_2O$ (metastable)
	50° Isothermal	
5·770	29·56	$CaH_4P_2O_8,H_2O$ and $CaHPO_4$

The solution saturated with respect to H_3PO_4 at 37·3° contained 71·30% of P_2O_5, while when both solid H_3PO_4 and $CaH_4P_2O_8$ were present at 37·35° the solution contained 71·52% of P_2O_5 and only a trace of CaO. At 35·75° in contact with saturated solution and solid H_3PO_4 there was also no tendency for $CaH_4P_2O_8$ to become hydrated. These facts indicate that the quintuple point with solid phases H_3PO_4, $CaH_4P_2O_8$, and $CaH_4P_2O_8,H_2O$ is not at 39° as originally suggested but probably at as low a temperature as 30°. The $CaH_4P_2O_8$–$CaH_4P_2O_8,H_2O$ boundary curve would then miss the solubility curve of $H_3P_2O_9$ by a reasonable margin before meeting that of H_3PO_4 at a point corresponding to 30° and 69·8% of P_2O_5 and a trace of CaO which may be taken as the co-ordinates of the quintuple point with solid phases H_3PO_4, $CaH_4P_2O_8$, and $CaH_4P_2O_8,H_2O$.

The Boiling Line.—Data are given in Table 4. The solubility of $Ca(OH)_2$ at 100° is that of coarse crystals and obtained from the solubility curve given by Bassett.[6] The figures for

[5] Geuther, *J. prakt. Chem.*, 1874, **8**, 359.

[6] Bassett, *J.*, 1934, 1270. (The reference to Shenstone and Cundall in line 8 from bottom of p. 1270 is given incorrectly and should be *J.*, 1888, **53**, 550.)

XUM

the basic phosphates are taken from Part IV [7] and those for the hydrogen orthophosphates from Part III [1] (where the CaO content of the solution boiling at 169° is given erroneously as 4·489% though the correct figure, 3·489%, was plotted).

TABLE 4.

Temp.	Solution CaO (%)	P_2O_5 (%)	Nature of solid phase
ca. 100°	0·517	—	$Ca(OH)_2$
,,	0·0501	Trace	$Ca(OH)_2$ and hydroxyapatite
,,	0·00001	0·000012	Hydroxyapatite
,,	0·0416	0·115	Hydroxyapatite and $Ca_3P_2O_8,xH_2O$
,,	0·0474	0·133	$Ca_3P_2O_8,xH_2O$ and $CaHPO_4$
115	5·623	43·60	$CaHPO_4$ and $CaH_4P_2O_8,H_2O$
132	4·327	53·43	$CaH_4P_2O_8,H_2O$ and $CaH_4P_2O_8$
169	3·489	63·95	$CaH_4P_2O_8$
200	2·404	67·29	$CaH_2P_2O_7$
220	1·950	69·56	$CaH_2P_2O_7$

The data for $CaH_2P_2O_7$ have not been published before. The value 220° is somewhat uncertain owing to superheating. The plot of boiling points against composition suggests that the boiling line cuts the boundary between the fields of $CaH_4P_2O_8$ and $CaH_2P_2O_7$ only a little above 169° and possibly at about 175°.

The solid phases from the experiments at 200° and 220° were obtained readily for analysis by filtration on asbestos in a small Buchner funnel and, after cooling, washing well with acetone and then ether (Found, at 200°: CaO, 26·12; P_2O_5, 65·56; loss on ignition 9·00. Found, at 220°: CaO, 25·97; P_2O_5, 65·56; loss on ignition 9·28. Calc. for $CaH_2P_2O_7$: CaO, 25·92; P_2O_5, 65·74; H_2O, 8·34%).

On heating there is partial melting and slight fuming owing to loss of P_2O_5 which accounts for the high loss on ignition. The crystals somewhat resemble those of $CaH_4P_2O_8,H_2O$ and $CaHPO_4,2H_2O$. The two mixtures had been prepared by boiling syrupy phosphoric acid in a silica flask until the desired boiling point was reached, whereupon $CaH_4P_2O_8,H_2O$ was added till present in small excess. A reflux condenser was then attached and boiling continued for 12 hr. The $CaH_2P_2O_7$ separated as well-formed small crystals after considerable supersaturation had occurred. This seems to be the first preparation of well-crystallised $CaH_2P_2O_7$, though a specimen with very little amorphous material has been obtained by thermal decomposition of $CaH_4P_2O_8$.[8]

The Space Model of the System $CaO–P_2O_5–H_2O$. We can now make the following deductions.

(1) The ice field is in two portions; a major one, strongly curved, rises almost vertically from the freezing-point curve (0° to −100°) of phosphoric acid solutions in the P_2O_5–temperature plane. This part of the field leans over very slightly in the direction of higher temperature. There is also a very small part of the ice field rising from the CaO–temperature plane above freezing-point curve (0° to −0·116°) of $Ca(OH)_2$ solutions. These two parts of the ice field are linked by the ice–hydroxyapatite curve which appears to pass through almost zero concentrations of CaO and P_2O_5 in the vicinity of 0°.

(2) The other boundaries of the ice field are given by the fields of $H_3P_2O_9$ (very short); $CaH_4P_2O_8,H_2O$; $CaHPO_4,2H_2O$; $Ca_3P_2O_8,xH_2O$; Hydroxyapatite; and $Ca(OH)_2$. The last three are all very short.

(3) The fields of $CaH_4P_2O_8,H_2O$ and of $CaH_4P_2O_8$ are concave in the $CaO–P_2O_5$ plane while the fields of $CaHPO_4,2H_2O$ and of $CaHPO_4$ are slightly convex in this plane.

(4) The highest CaO concentrations occur along the boundary between the regions of mono- and di-calcium phosphate which forms a well marked ridge on the space model. The maximum concentration (6·1% of CaO) occurs at the ice–$CaH_4P_2O_8,H_2O$–$CaHPO_4,2H_2O$ quintuple point. It falls off very slowly in the direction of higher temperature, the value 5·6% of CaO being reached at 152°. The P_2O_5 values along this ridge increase from 19·62% at −7·5° to 53·00% at 152°.

[7] Bassett, *J.*, 1917, **111**, 620.
[8] Hill, Hendricks, Fox, and Cady, *Ind. Eng. Chem.*, 1947, **39**, 1667.

XUM

(5) The solubility of monocalcium phosphate falls off rapidly with increasing concentrations of phosphoric acid so that the fields of solid $H_8P_2O_9$ and H_3PO_4 have hardly any width. In the case of $H_8P_2O_9$ the CaO content along the $H_8P_2O_9$–$CaH_4P_2O_8,H_2O$ curve reaches to just over 0·2% but along the H_3PO_4–$CaH_4P_2O_8$ curve it amounts to a mere trace.

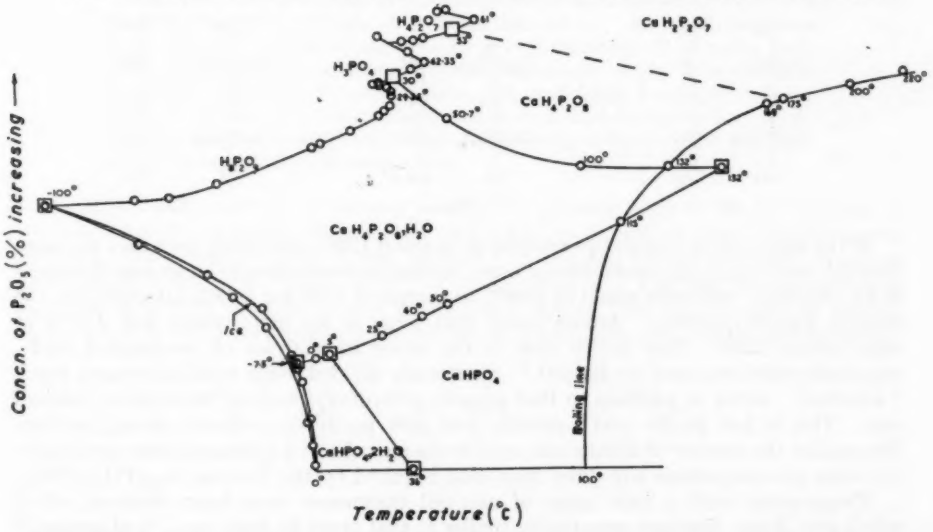
(6) The quintuple point with solid phases H_3PO_4, $CaH_4P_2O_8$, and $CaH_4P_2O_8,H_2O$ is probably at 30° and not at 39° as originally indicated.

(7) It is suggested that the boundary between the fields of $CaH_4P_2O_8$ and $CaH_2P_2O_7$ runs from a point at about 175° on the boiling line to a point at about 53° on the solubility curve of $H_4P_2O_7$.

(8) It is still uncertain whether tricalcium phosphate occurs in the CaO–P_2O_5–H_2O system [9] but, as the 1917 experiments [7] seemed to show that it did, we still consider it to be one of the compounds which occur at low concentrations of CaO and P_2O_5. The case of tetracalcium phosphate is, however, different and there seems to be no real evidence for its occurrence in, at any rate, aqueous calcium phosphate systems.*

(9) It is not easy to determine the exact temperature of quintuple points, especially those at low temperatures, owing to the slowness of the reactions involved. It has been suggested [10] that the one at 36° (solid phases $CaHPO_4,H_2O$, $CaHPO_4$, and probably $Ca_3P_2O_8,xH_2O$) may occur at a rather higher temperature, which may be 40°. The

Space model of the system CaO–P_2O_5–H_2O *projected upon the temperature–*P_2O_5 *plane (to scale).*



dilatometer is not very satisfactory, but a definite though slow expansion could be measured at as low a temperature as 36·4°.[1] The temperature 36° would only apply to the three-component system and the use of salt solutions to test the matter as in Lugg's work does not seem justified since the presence of other components could cause profound changes.

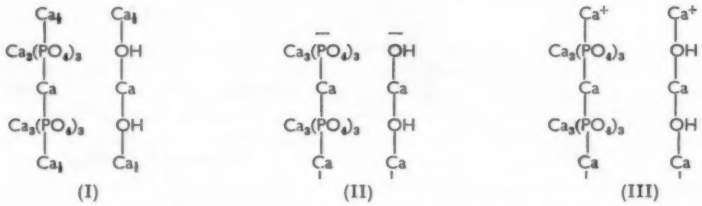
* [*Added in Proof*, 21.6.58.]—In an important recent paper on calcium orthophosphates Niels Bjerrum (*Kgl. danske Videnskab. Selskab. Mat.-fys. Medd.*, 1958, **31**, No. 7, 1—79) considers very fully the difficult problem of tricalcium phosphate and hydroxyapatite. It appears that anhydrous $Ca_3P_2O_8$, first obtained from high temperature fusions by Trömel (*Mitt. Kaiser Wilh. Inst. Eisenforsch.*, 1932, **14**, Abh. 198), has since been found in the low-temperature β-form as "stones" from the bladder and other parts of the human body. β-$Ca_3P_2O_8$ has also been found as a mineral, Whitlockite, by Frondel (*Amer. Mineralog.*, 1941, **26**, 145; 1943, **28**, 215).

[9] D'Ans and Knütter, *Angew. Chem.*, 1953, **65**, 578.
[10] Lugg, *Trans. Faraday Soc.*, 1931, **27**, 297.

At present therefore this quintuple point is considered to be at 36° (with CaO, 0·0514%; P_2O_5, 0·140%) though it may be somewhat lower, not higher.

(10) It seems likely that 21° as determined in 1908 [1] is considerably too high for the quintuple point at which the three solid phases are $CaH_4P_2O_8,H_2O$, $CaHPO_4,2H_2O$, and $CaHPO_4$. The much lower temperature makes the dilatometer even more unsatisfactory. With continuous shaking a suitable mixture of $CaH_4P_2O_8,H_2O$, $CaHPO_4,2H_2O$, and solution will change completely to one of $CaH_4P_2O_8,H_2O$, $CaHPO_4$, and solution during several days at 25°, whereas much longer is required at 0° for the corresponding change in which $CaHPO_4$ is converted into $CaHPO_4,2H_2O$. At 15° the mixture containing $CaHPO_4$ was also more stable than that containing $CaHPO_4,2H_2O$ while the temperature of equal stabilities was at 5° as nearly as could be determined. We thus consider 5° to be correct for this quintuple point (with CaO, 5·98%; P_2O_5, 21·00%). The region of $CaHPO_4,2H_2O$ on the space model will have only about three-quarters of the area shown on the diagram of 1908.

(11) Arnold [11] has thrown much light upon the hydroxyapatite problem. He points out that the unit cell of hydroxyapatite $[Ca_{10}(PO_4)_6(OH)_2]$ can be represented most simply by (I). For an exposed surface the position may be represented by (II) or (III) according to whether the surface column Ca is absent or present; the latter is the most likely in neutral or alkaline solutions when the positive charges would be neutralised by hydroxyl ions.



If the surface hydroxyl groups are held up to about 1230°, as is likely since they are more than 5 Å apart, the total constitutional water content corresponding to an average thickness of 13 " apatite " unit cells would be 2·06% as compared with the 1·79% calculated for the formula $Ca_{10}(PO_4)_6(OH)_2$. Arnold found that some of his preparations lost 2·07% of water above 1230°. This is also close to the deficit in analyses of precipitated hydroxyapatite solids reported by Bassett.[7] Such finely divided solids would also carry much " adsorbed " water in addition to that present as hydroxyl ions on the exposed calcium ions. This is lost partly over sulphuric acid and partly on ordinary strong ignition. The smaller the number of apatite unit cells in the particles of a hydroxyapatite precipitate the more its composition will differ from that required by the formula $Ca_{10}(PO_4)_6(OH)_2$.

Preparations with a wide range of unit-cell thicknesses have been obtained, all of which give *X*-ray diagrams remarkably similar to that given by large crystals of apatite.[11]

(12) It is impossible to show the basic region of the $CaO–P_2O_5–H_2O$ system to scale on the same diagram as the rest of the system. The areas and concentrations involved are so small that the whole basic region would only appear on the space model as a very low sharp edge rising vertically above the temperature–P_2O_5 plane along the axis of temperature. The maximum height of this would occur at −0·116° with 0·130% of CaO at the cryohydric point for coarse crystals of $Ca(OH)_2$.[7]

The solubility of $Ca(OH)_2$ falls off rapidly with increasing temperature and is 0·0523% of CaO at 99° and 0·0246% of CaO at 150°.[12] The above-mentioned sharp edge would subside in the same way. It is difficult to say just what effect this would have on the areas of hydroxyapatite and $Ca_3P_2O_8,xH_2O$. Their " alkaline " region would be greatly

[11] Arnold, *Trans. Faraday Soc.*, 1950, **46**, 1061.
[12] Shenstone and Cundall, *J.*, 1888, **53**, 550.

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restricted but owing to increased hydrolysis at higher temperatures they would probably spread into regions of higher P_2O_5 : CaO ratios, as happens to $CaHPO_4,2H_2O$ and $CaHPO_4$.

(13) The diagram presented is true to scale and is a projection of the space model of the system $CaO–P_2O_5–H_2O$ upon the temperature–P_2O_5 plane. Squares indicate quintuple points. It is not considered necessary to give a sketch of the solid model which is really very simple. It can be regarded as a double wedge sloping downwards from a central ridge in two directions. There is a convex slope in the direction of decreasing P_2O_5 and a concave slope in the direction of increasing P_2O_5. There is in addition a third general downward slope in the direction of increasing temperature and away from the almost vertical ice field.

THE UNIVERSITY, READING. [*Received, March 19th*, 1958.]

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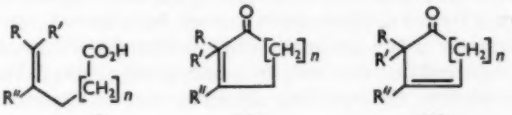
602. *Reduced Cyclic Compounds. Part IV.* The Intramolecular Acylation of Some Olefinic Acids.*

By M. F. ANSELL and S. S. BROWN.

Intramolecular acylation, in polyphosphoric acid, of the six alkenoic acids $R{\cdot}CH{=}CH{\cdot}CH_2{\cdot}[CH_2]_n{\cdot}CO_2H$ (R = H or Me; n = 1, 2, or 3) has been shown to give (except where R = H, n = 1) mixtures of isomeric *cyclo*pentenones and *cyclo*hexenones. Similar treatment of the three alkenoic acids $Me_2C{=}CH{\cdot}CH_2{\cdot}[CH_2]_n{\cdot}CO_2H$ (n = 1, 2, or 3) gives 3-methyl*cyclo*hex-2-enone, a mixture of 2-*iso*propyl*cyclo*pent-2-enone and 2-*iso*propylidene*cyclo*pentanone, and a mixture containing 2-*iso*propyl*cyclo*hex-2-enone and 2-*iso*propylidene*cyclo*hexanone respectively.

INTRAMOLECULAR acylation of suitably constituted alkenoic acids [1,2] (or the lactones of the related hydroxy-acids) and alkenoyl chlorides [3] is known to yield *cyclo*alkenones. Attention has previously been chiefly directed [4] to the ring closure of highly branched structures such as (I; R = H, R′ and R″ = alkyl or aryl; n = 1 or 2) to the corresponding *cyclo*alkenones (II); if both R and R′ are alkyl groups, the ketone (III) is formed. Hitherto the scope of the intramolecular acylation, particularly with respect to the relative



(I) (II) (III)

ease of formation of *cyclo*pentanone and *cyclo*hexanone derivatives, has not been defined. The preparation of *cyclo*heptanone derivatives by this route is not recorded. We have, therefore, examined the intramolecular acylation of the acids [I; (*a*) R = R′ = R″ = H, n = 1, 2, or 3; (*b*) R = Me, R′ = R″ = H, n = 1, 2, or 3; and (*c*) R = R′ = Me, R″ = H, n = 1, 2, or 3], the preparation of which has been described elsewhere.[5]

Reaction of pent-4-enoyl chloride and *trans*-hex-4-enoyl chloride with aluminium

* Part III, *J.*, 1958, 1167.

[1] (*a*) Maschmeijer, F.P. 765,515/1934); (*b*) Plattner and St. Pfau, *Helv. Chim. Acta*, 1937, **20**, 1474; (*c*) Rai and Dev, *J. Indian Chem. Soc.*, 1957, **34**, 178, and references there cited.

[2] Burnop, Elliot, and Linstead, *J.*, 1940, 727.

[3] Cook and Lawrence, *J.*, 1935, 1637; 1937, 817; Chuang, Tien, and Ma, *Ber.*, 1936, **69**, 1494.

[4] *Inter al.*, Johnson, Johnson, and Peterson, *J. Amer. Chem. Soc.*, 1945, **67**, 1360; 1946, **68**, 1926; Johnson and Peterson, *ibid.*, 1945, **67**, 1366.

[5] Ansell and Brown, *J.*, 1957, 1788.

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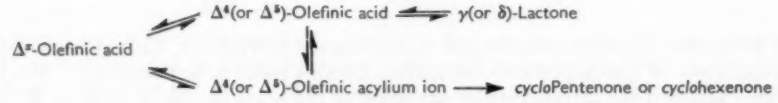
chloride in boiling carbon disulphide (cf. ref. 6) gave *cyclo*pent-2-enone (30%) and 2-methyl-*cyclo*pent-2-enone (50%) respectively. Hex-5-enoyl chloride, under these conditions, gave a small amount of *cyclo*hex-2-enone, together with a chloro-ketone (possibly 3-chloro*cyclo*hexanone). Cyclisation of *trans*-hept-5-enoyl chloride gave a heterogeneous chlorine-containing ketone. In view of the difficulties in obtaining chlorine-free cyclization products from the alkenoyl chlorides, a study was made of the action of polyphosphoric acid on the free alkenoic acids.[7]

With the exception of pent-4-enoic acid, each of the six straight-chain acids (I*a* and *b*) with polyphosphoric acid gave heterogeneous products from which ketonic and lactonic components were isolated, the proportions varying according to the reaction conditions (see Table 1). No systematic attempts were made to identify the lactones in view of the paucity of reference compounds, but the ketones were identified.

Attempted cyclization of pent-4-enoic acid gave no detectable amount of ketone. γ-Valerolactone was the only volatile product. This is to be compared with the failure by Frank *et al.*[8] to effect intramolecular acylation of γ-valerolactone by use of phosphoric oxide, and with Ferrier and Tedder's observation [9] that treatment of the acid with trifluoroacetic anhydride gave only a trace of *cyclo*pent-2-enone together with " a linear dimer." *trans*-Hex-4-enoic acid with an excess of hot polyphosphoric acid gave 2-methyl*cyclo*pent-2-enone (40%), which, together with a trace of *cyclo*hex-2-enone, was also obtained from hex-5-enoic acid under the same conditions. Ferrier and Tedder,[9] using trifluoroacetic anhydride, obtained *cyclo*hex-2-enone from hex-5-enoic acid in 46% yield. Cyclisation of hept-6-enoic and *trans*-hept-5-enoic acid gave virtually identical mixtures of 2-methyl*cyclo*hex-2-enone and 2-ethyl*cyclo*pent-2-enone. Similarly, *trans*-oct-6-enoic acid gave a mixture of 2-ethyl*cyclo*hex-2-enone and 2-*n*-propyl*cyclo*pent-2-enone.

The three acids of class (I*c*) behaved rather differently to the unsubstituted acids on treatment with polyphosphoric acid. 5-Methylhex-4-enoic acid gave only 3-methyl*cyclo*hex-2-enone; 6-methylhept-5-enoic acid gave a mixture of 2-*iso*propylidene*cyclo*pentanone and 2-*iso*propyl*cyclo*pent-2-enone; 7-methyloct-6-enoic acid gave a mixture of unsaturated ketones from which derivatives of 2-*iso*propylidene*cyclo*hexanone and 2-*iso*propyl*cyclo*hex-2-enone were isolated. No lactonic material was found.

These results, together with the known [10] formation of mixtures of *cyclo*alkenones from undec-10-enoic acid, 4-methyldec-9-enoic acid, and dec-9-enoic acid, may be rationalised by assuming that, under strongly acid conditions, the double bond of an alkenoic acid is highly labile, by virtue of carbonium-ion formation, and may migrate to a suitable position for electrophilic attack by the acylium ion [10] derived from the carboxyl group of the same molecule. Concomitantly a lactone–enoic acid equilibrium [11,12] must be set up. Since the experimental results indicate that only five- and/or six-membered rings may be formed by intramolecular acylation, the equilibria obtaining may be depicted as:



The absence of isolable amounts of *cyclo*pent-2-enone and *cyclo*hex-2-enone in the cyclisation products of pent-4-enoic and hex-5-enoic acid respectively, is undoubtedly due, not to the fact that intramolecular acylation does not occur, but to very ready polymerisation of these ketones under the reaction conditions. *cyclo*Alkenones having α-alkyl

[6] Gutsche and Johnson, *J. Amer. Chem. Soc.*, 1946, **68**, 2239.
[7] Cf. Dev, *Chem. and Ind.*, 1954, 1071; *J. Indian Chem. Soc.*, 1955, **32**, 255.
[8] Frank, Armstrong, Kwiatek, and Price, *J. Amer. Chem. Soc.*, 1948, **70**, 1379.
[9] Ferrier and Tedder, *J.*, 1957, 1435.
[10] Baddeley, *Quart. Rev.*, 1954, **8**, 355.
[11] Linstead and Rydon, *J.*, 1934, 1995.
[12] Johnson and Hunt, *J. Amer. Chem. Soc.*, 1950, **72**, 935; Mathieson, *J.*, 1951, 177.

substituents are evidently less susceptible to cationic polymerisation, so that there is no difficulty in isolating such ketones in these cases. The higher straight-chain acids give *mixtures* of isomeric ketones (in conflict with a recent report [13]), which much reduces the preparative value of their intramolecular acylation.

TABLE 1. *Intramolecular acylations with polyphosphoric acid.*

	Conditions		Lactonic product		Ketonic product	
Acid	Temp.	Time (min.)	B. p. mm.	Yield (%)	B. p. mm.	Yield (%)
Pent-4-enoic	100°	10	80—81°/12	22		0
trans-Hex-4-enoic	100	120	93—98°/12	48	51—52°/12	9
	120	7		24		38
	130	30		35		30
	140	15		30		24
Hex-5-enoic	80	100	102—104°/15	17	52—54°/15	7·2
	90	20		18		8·4
	100	10		40		9·6
	110	5		5·3		0
trans-Hept-5-enoic	85	60	112—117°/15	22	74—75°/24	51
	90	15		21		52
	95	40		13		55
	100	30		9·5		41
	105	30		2·1		16
Hept-6-enoic	90	30	115—120°/16	9	74—75°/24	37
	95	15		12		53
	100	15		17		57
	110	10		16		57
trans-Oct-6-enoic	90	25	120—127°/16	9·5	89—91°/24	57
	95	15		1·3		54
	100	10		2·0		47
5-Methylhex-4-enoic	90	30		0	94—95°/24	73
	110	15		0		77
6-Methylhept-5-enoic	80	10		0	80—84°/14	33
	100	5		0		38
7-Methyloct-6-enoic	95	15		0	48—50°/1	6
	85	5		0		9

Cyclisation of the three branched-chain acids (Ic) was accompanied by extensive polymerisation; a good yield of *cyclo*alkenone was indeed only obtained from 5-methylhex-4-enoic acid, which enters exceptionally readily [11] into the lactone–enoic equilibrium. Intramolecular acylation of this acid, which may be visualized as proceeding through the "*iso*propenyl isomer," 5-methylhex-5-enoic acid, finds precedents in the formation of substituted 3-methyl*cyclo*hex-2-enones from 4-methyl-4-*iso*propyl-γ-butyrolactone,[8] dihydrolavandulic acid,[14] and (2-methylallyl)succinic anhydride.[15] In contrast, in the cyclization of 6-methylhept-5-enoic acid both steric and electronic factors are favourable to the formation of a *cyclo*pentanone derivative. Although both 2-*iso*propylidene*cyclo*pentanone and 2-*iso*propyl*cyclo*pent-2-enone are actually formed, the former is probably the primary cyclization product [16] since an authentic specimen was found to be largely isomerized to the endocyclic isomer by hot polyphosphoric acid. Similarly, it is likely that 2-*iso*propylidene*cyclo*hexanone is the primary product of the intramolecular acylation of 7-methyloct-6-enoic acid; this reaction is analogous to the ring closure [17] of citronellyl chloride to (±)-pulegone.

EXPERIMENTAL

Refractive indices are for the Na_D line at 20° unless otherwise stated. Fractional distillations marked (S) were effected with a spinning-band semimicro-fractionating column (E. Haage,

[13] Dominquez, Diaz, and Slim, *Ciencia*, 1957, **16**, 151.
[14] Kuhn and Schinz, *Helv. Chim. Acta*, 1953, **36**, 161.
[15] Phillips and Johnson, *J. Org. Chem.*, 1956, **21**, 587.
[16] Cf. Eschenmoser, Shinz, Fischer, and Colonge, *Helv. Chim. Acta*, 1951, **34**, 2329.
[17] Bardhan and Bhattacharyya, *Chem. and Ind.*, 1951, 800.

Mulheim). Ultraviolet absorption spectra refer to 95% EtOH solutions. Hydrogenations were carried out at atmospheric pressure in ethanol solution over Adams catalyst. The acid chlorides were prepared with a 10% molar excess of thionyl chloride and a catalytic amount of pyridine in boiling ether and were distilled immediately before use.

Cyclisation of Pent-4-enoyl Chloride.—A stirred suspension of powdered aluminium chloride (33 g., 0·26 mole) in boiling carbon disulphide (130 ml.) was treated dropwise with pent-4-enoyl chloride (26 g., 0·22 mole) during 30 min. An exothermic reaction occurred and hydrogen chloride was evolved; after a further 1 hr. under reflux the mixture was poured on ice (150 g.), and sufficient concentrated hydrochloric acid (*ca.* 20 ml.) was added to dissolve the precipitate. The organic layer was separated and the aqueous layer extracted with carbon disulphide (2 × 80 ml.). The combined extracts were washed successively with 50 ml. portions of 5% hydrochloric acid, brine, saturated sodium hydrogen carbonate solution, and brine. Distillation of the dried ($MgSO_4$) extract gave *cyclo*pent-2-enone (0·4 g.), b. p. 50—55°/25 mm. The aqueous residues from the above extraction were combined and continuously steam-distilled and ether-extracted (Vogel [18]). The residue obtained on evaporation of the dried ($MgSO_4$) extract was distilled, yielding *cyclo*pent-2-enone (6·4 g.), b. p. 56—58°/24 mm. The redistilled cyclization product had n 1·4818, $\lambda_{max.}$ 218, mμ (log ε 3·86), and formed a semicarbazone (laths from aqueous ethanol), m. p. 212—213°, and a 2 : 4-dinitrophenylhydrazone (red needles from ethanol), m. p. 170—171°. The reported values for *cyclo*pent-2-enone are: b. p. 42°/11 mm., n 1·4813 (ref. 19) $\lambda_{max.}$ 218 (log ε 3·99) (ref. 20), semicarbazone, m. p. 214—215° (refs. 21, 22) or 217—218° (ref. 23), 2 : 4-dinitrophenylhydrazone, m. p. 169—170° (ref. 23).

Cyclisation of trans*-Hex-4-enoyl Chloride.*—Cyclisation of this chloride (12 g., 0·091 mole) was effected as in the previous experiment. Evaporation of the carbon disulphide extract gave a chlorine-containing material which lost hydrogen chloride on distillation to give a ketonic product (4·1 g.), b. p. 60—64°/24 mm. A further 0·5 g. of ketone was obtained by continuous steam-distillation and ether-extraction (Vogel [18]) of the aqueous solutions. Redistillation of the combined material gave 2-methyl*cyclo*pent-2-enone, b. p. 53—54°/15 mm., n 1·4780. The derived semicarbazone and 2 : 4-dinitrophenylhydrazone had m. p.s 218—220° (decomp.) and 221—222° respectively. For previously recorded constants see the cyclisation of *trans*-hex-4-enoic acid below.

Cyclisation of Hex-5-enoyl Chloride.—The cyclisation of this chloride (10 g., 0·075 mole) was effected as above. Evaporation of the carbon disulphide extract yielded a chlorine-containing material which was distilled at 1 mm., with very little decomposition, to yield fractions: (1) b. p. <40°, 0·5 g.; (2) b. p. 40—58°, n 1·4871, 0·6 g.; (3) b. p. 58—59°, n 1·4867, 1·6 g.; (4) b. p. 59—60°, n 1·4867—1·4861, 4·3 g. The 2 : 4-dinitrophenylhydrazones from fractions 1 and 2 were clearly heterogeneous but the former, after chromatography (in benzene–hexane on alumina), yielded the 2 : 4-dinitrophenylhydrazone of *cyclo*hex-2-enone whose m. p., 162—163°, was not depressed in admixture with an authentic sample,[24] m. p. 165—167° (Rigby [25] records m. p. 164—165°).

Fraction (4) was redistilled (b. p. 59—60°/1 mm.; n 1·4867) (Found: C, 55·3; H, 6·6; Cl, 25·8. Calc. for C_6H_9OCl: C, 54·3; H, 6·8; Cl, 26·8%) and gave a semicarbazone (plates from water), m. p. 165—166° (Found: C, 44·7; H, 6·4; Cl, 18·0; N, 22·3. Calc. for $C_7H_{12}ON_3Cl$: C, 44·3; H, 6·4; Cl, 18·7; N, 22·1%), and a 2 : 4-dinitrophenylhydrazone (plates from ethanol–chloroform), m. p. 139—140° (Found: C, 46·1; H, 4·6; Cl, 11·3; N, 18·2. Calc. for $C_{12}H_{13}O_4N_4Cl$: C, 46·1; H, 4·2; Cl, 11·3; N, 17·9%). These data do not correspond with those for 2- or 4-chloro*cyclo*hexanone;[26a] derivatives of 3-chloro*cyclo*hexanone[26b] have not been reported.

[18] Vogel, " Practical Organic Chemistry," Longmans Green, London, 1951, p. 223.
[19] Alder and Flock, *Chem. Ber.*, 1956, **89**, 1732.
[20] Schubert and Sweeney, *J. Amer. Chem. Soc.*, 1955, **77**, 2297.
[21] Godchot and Taboury, *Compt. rend.*, 1913, **156**, 333.
[22] Nazarov, Bergelson, Torgov, and Ananchenko, *Bull. Acad. Sci. U.S.S.R.*, 1953, 889; *Chem. Abs.*, 1955, **49**, 1082.
[23] Mousseron, Jacquier, and Fontaine, *Bull. Soc. chim. France*, 1952, **19**, 767.
[24] Born, Pappo, and Szmuszkovicz, *J.*, 1953, 1779.
[25] Rigby, *J.*, 1949, 1586.
[26] (*a*) Meyer, *Helv. Chim. Acta*, 1933, **16**, 1291; Ramirez and Kirby, *J. Amer. Chem. Soc.*, 1952, **74**, 4331; Campbell and McCall, *J.*, 1950, 2870; Sabetay and Palfray, *Bull. Soc. chim. France*, 1928, **43**, 906; Grewe, Lorenzen, and Vining, *Chem. Ber.*, 1954, **87**, 793; (*b*) Kotz and Grethe, *J. prakt. Chem.*, 1909, **80**, 503.

Cyclisation of trans-*Hept-5-enoyl Chloride.*—This chloride (18 g.) was cyclised as above. Evaporation of the carbon disulphide extract gave a chlorine-containing product (10 g.) which partially decomposed on distillation (b. p. 38—41°/0·5 mm.; n 1·4794) and was not obtained analytically pure. It gave heterogeneous derivatives, but by persistent recrystallisation, the 2 : 4-dinitrophenylhydrazone (yellow needles from benzene), m. p. 181—182° (Found: Cl, 10·4; N, 17·5. Calc. for $C_{13}H_{15}O_4N_4Cl$: Cl, 10·9; N, 17·1%), and the semicarbazone (plates from water), m. p. 182—183° (Found: N, 20·6; Cl, 17·5. Calc. for $C_8H_{14}ON_3Cl$: N, 20·6; Cl, 17·4%), possibly of 3-chloro-2-methyl*cyclo*hexanone, were obtained.

General Procedure for Cyclisation of the Olefinic Acids—Polyphosphoric acid [27] (100 g.) was stirred gently (so as not to break the surface of the liquid) and heated to the required temperature. The alkenoic acid (0·1 mole) was added in one portion and the mixture stirred and heated as before. The acid, at first having formed an upper layer, quickly dissolved and the mixture became first orange-red, then brown. After the requisite time, the mixture was cooled rapidly to 30° and ice (*ca.* 150 g.) added. The product was extracted with ether (3 × 70 ml.), either manually, or by the continuous steam distillation–ether extraction process (Vogel [18]). The extract was washed successively with saturated brine, saturated sodium hydrogen carbonate solution, and brine. After drying ($MgSO_4$), the solvent was removed through a short column and the residue separated by distillation into ketonic and lactonic fractions (see Table 1).

Cyclisation of Pent-4-enoic Acid.—No ketonic material was obtained and the lactonic material (n 1·4342) was identified as γ-valerolactone, the m. p. (66—67°) of the derived hydrazide not being depressed in admixture with an authentic specimen, m. p. 67—68°. The derived S-*benzylthiuronium salt* (rhombs from acetone) had m. p. 138—139° (Found: N, 9·8; S, 11·1. $C_{13}H_{20}O_2N_2S$ requires N, 9·85; S, 11·3%). Linstead and Rydon [28] record b. p. 88°/15 mm., n 1·4315. Reppe *et al.*[29] record a hydrazide, m. p. 67—68°.

Cyclisation of trans-*Hex-4-enoic Acid.*—Distillation of the combined ketonic material gave only 2-methyl*cyclo*pent-2-enone, b. p. 51—52°/13 mm., n 1·4798—1·4810, $\lambda_{max.}$ 226, 309, $\lambda_{min.}$ 268 mμ (log ε 3·92, 14·7, 0·89) [oxime (needles from ethanol), m. p. 127—128°; semicarbazone (tablets from ethanol), m. p. 219—220° (decomp.); 2 : 4-*dinitrophenylhydrazone* (red tablets from chloroform), m. p. 221—222° (Found: N, 20·1. $C_{12}H_{12}O_4N_4$ requires N, 20·3%)]. Nazarov *et al.*[22] record b. p. 52—53°/15 mm., oxime, m. p. 128°, and semicarbazone, m. p. 218° (decomp.). Hydrogenation gave 2-methyl*cyclo*pentanone [30] [semicarbazone (prisms from methanol), m. p. and mixed m. p. 177—178°; 2 : 4-dinitrophenylhydrazone (orange plates from ethanol–chloroform), m. p. and mixed m. p. 159—160°].

Cyclisation of Hex-5-enoic Acid.—Redistillation of the ketonic fraction gave material, b. p. 52—54°/15 mm., n 1·4773, $\lambda_{max.}$ 226 and 310, $\lambda_{min.}$ 269 mμ (log ε 3·75, 1·33, 0·92), which yielded the semicarbazone, prisms, m. p. 220—221° (after three recrystallisations from aqueous ethanol), and the 2 : 4-dinitrophenylhydrazone, red tablets, m. p. 221—222° (after one recrystallisation from ethanol–chloroform), of 2-methyl*cyclo*pent-2-enone (see previous experiment for reported constants). Hand-sorting of the crystals obtained on evaporation of the mother-liquors from the 2 : 4-dinitrophenylhydrazone gave the 2 : 4-dinitrophenylhydrazone of *cyclo*hex-2-enone (orange laths), whose m. p. (160—162°) was not depressed on admixture with an authentic sample [24] of m. p. 165—167°.

Cyclisation of trans-*Hept-5-enoic Acid.*—Distillation(S) of the combined ketonic material gave 11 fractions (each of 1·0 ml.), b. p. 74—75°/24 mm., n 1·4810—1·4780. The m. p.s of the derivatives (after two recrystallisations) of fractions (2), b. p. 74—74·5°/24 mm., n 1·4816, and (11), b. p. 74·5—75°/24 mm., n 1·4780, suggested that they were predominantly 2-methyl*cyclo*hex-2-enone and 2-ethyl*cyclo*pent-2-enone respectively. This was supported by mixed m. p. determinations with the derivatives of the original fractions and of the hydrogenated material (see Table 2.).

Cyclisation of Hept-5-enoic Acid.—Distillation (S) of the combined ketonic material gave 13 fractions (each of 0·6 ml.), b. p. 74—75·5°/24 mm., n 1·4823—1·4776. The derivatives of fractions (2), b. p. 74—74·5°/24 mm., n 1·4823, and (13), b. p. 74·5—75·5°/24 mm., n 1·4776 (after two recrystallisations), were respectively identical with those from fractions (2) and (11) from the cyclisation of *trans*-hept-5-enoic acid (see Table 2).

[27] Uhlig, *Angew. Chem.*, 1954, **66**, 435.
[28] Linstead and Rydon, *J.*, 1933, 580.
[29] Reppe, Kröper, Pistor, and Weissbarth, *Annalen*, 1953, **582**, 87.
[30] Cornubert and Borrel, *Bull. Soc. chim. France*, 1930, **47**, 301.

XUM

TABLE 2.

Ketone	2 : 4-Dinitrophenylhydrazone (m. p.) Obtained	Authentic	Semicarbazone (m. p.) Obtained	Authentic
2-Methyl*cyclo*hex-2-enone	191—192° [a]	206—207° [c]	199—201° [a]	205—206°
	189—192 [b]	—	200—201 [b]	—
2-Methyl*cyclo*hexanone	127—129	133—134 [d]	167—170	185—186 [d]
2-Ethyl*cyclo*pent-2-enone	216—217 [a]	219—220 [e]	196—198 [a]	—
	218—219 [b]	—	198—200 [b]	—
2-Ethyl*cyclo*pentanone	154—156	157—160 [f, g]	172—175	183—184 [f]

[a] From cyclisation of *trans*-hept-5-enoic acid. [b] From cyclisation of hept-6-enoic acid (see below). [c] Ref. 24. [d] From commercial ketone. [e] From the ketone obtained by reaction of 2-ethyl*cyclo*pentanone with sulphuryl chloride.[31] The *derivative* formed crimson laths from ethanol–chloroform (Found: C, 53·7; H, 4·6. $C_{13}H_{14}O_4N_4$ requires C, 53·8; H, 4·9%). [f] From the ketone prepared by hydrolysis of ethyl 1-ethyl-2-oxo*cyclo*pentanecarboxylate.[32] [g] Golden prisms from ethanol (Found: N, 18·8. $C_{13}H_{14}O_4N_4$ requires N, 19·2%).

Cyclisation of trans-*Oct-5-enoic Acid.*—Distillation (S) of the combined ketonic material gave 16 fractions (each of 0·7 ml.), b. p. 88—91°/24 mm., n 1·4783—1·4744. Fraction (4), b. p. 89—89·5°/24 mm., n 1·4826, gave a 2 : 4-dinitrophenylhydrazone, m. p. 233—234°, and semicarbazone, m. p. 181—182°, identical with those of 2-ethyl*cyclo*hex-2-ene prepared from the enol *iso*butyl ether of 2-ethyl*cyclo*hexane-1 : 3-dione by the method of Born *et al.*[24] (for previous constants see ref. 34). Fraction 11, b. p. 90—90·5°/24 mm., n 1·4778, was accepted as 2-n-*propyl*cyclo*pent-2-enone* on the basis of its analyses (Found: C, 77·1; H, 9·5. $C_8H_{12}O$ requires 77·4; H, 9·7%) [2 : 4-*dinitrophenylhydrazone*, laths, m. p. 177—178°, from ethanol–chloroform (Found: C, 54·8; H, 5·2. $C_{14}H_{16}O_4N_4$ requires C, 55·25; H, 5·3%); *semicarbazone*, plates, m. p. 217—218°, from ethanol (Found: N, 23·0. $C_9H_{15}ON_3$ requires N, 23·2%], its ultraviolet spectrum [$\lambda_{max.}$ 228, 319, $\lambda_{min.}$ 278 mμ (log ε 4·03, 1·62, and 1·09)], and hydrogenation to 2-*n*-propyl*cyclo*pentanone [35] which was identified (mixed m. p.s) as 2 : 4-dinitrophenylhydrazone, m. p. 154—155°, and semicarbazone, m. p. 206—207°.

Cyclisation of 5-*Methylhex-5-enoic Acid.*—Distillation (S) of the combined ketonic material gave the following fractions, each of 0·7 ml.: (1, 2), b. p. 93—95°/24 mm., n 1·4890—1·4918; (3—14), b. p. 95—95·5°/24 mm., n 1·4930—1·4942. The ultraviolet spectra [$\lambda_{max.}$ 224 and 310, $\lambda_{min.}$ 227 mμ (log ε 4·13, 1·79, 1·33)] of fractions (3) and (13) were identical with each other and with that of an authentic specimen of 3-methyl*cyclo*hex-2-enone.[36] The m. p.s of the derived semicarbazone (m. p. 197—198°) and 2 : 4-dinitrophenylhydrazone (m. p. 178—179°) were not depressed in admixture with authentic derivatives.

Cyclisation of 6-*Methylhept-5-enoic Acid.*—Distillation of the combined ketonic material gave 5 fractions, each of 0·9 ml.: b. p. 80—84°/13 mm., n 1·4817—1·4878. The properties of

TABLE 3.

	Fraction (1)	A [a]	Fraction (5)	B [d]
B. p./mm.	80—81°/13	84·5—85°/24	83—84°/13	91·5—92°/24
n	1·4817	1·4722	1·4878	1·4855
$\lambda_{max.}$ (mμ) (log ε)	229 (4·07)	225 (4·24)	243 (3·74)	255 (4·10)
Semicarbazone, m. p.	200—206°	204—206° [b]	210—213° [e]	216—217° [e]
2 : 4-Dinitrophenylhydrazone, m. p. ...	207—209° [e]	202—203° [c, e]	216—218° [e]	226—227° [e, c]

[a] With decomp. [b] Prepared by isomerisation of 2-*iso*propylidene*cyclo*pentanone with polyphosphoric acid at 100°. [c] Meerwein [38] reports m. p. 203—204°. [d] Red needles from ethanol–chloroform (Found: N, 18·2. $C_{14}H_{14}O_4N_4$ required N, 18·4%). [e] Reported [39] b. p. 92°/20 mm., n^{18} 1·4968. [e] Maroon laths from ethanol–chloroform (Found: C, 55·5; H, 5·1. $C_{14}H_{16}O_4N_4$ requires C, 55·25; H, 5·3%).

fractions (1), b. p. 80—81°/13 mm., n 1·4817, and (5) b. p. 83—84°/13 mm., n 1·4878, and of their derivatives (after two recrystallisations), are compared in Table 3 with those of authentic 2-*iso*propyl*cyclo*pent-2-enone (A) and 2-*iso*propylidene*cyclo*pentanone [37] (B).

[31] Cf. Warnhoff and Johnson, *J. Amer. Chem. Soc.*, 1953, **75**, 94.
[32] Case and Reid, *ibid.*, 1928, **50**, 3062.
[33] Stetter and Dierichs, *Chem. Ber.*, 1952, **85**, 61; Smith, *J.*, 1953, 803.
[34] Birch, *J. Proc. Roy. Soc. New South Wales*, 1949, **83**, 245; Mousseron and Jacquier, *Bull. Soc. chim. France*, 1952, **19**, 767; Jaeger and Smith, *J.*, 1955, 160; Wallach and Mendelsohn-Bartholdy, *Annalen*, 1908, **360**, 48.
[35] Braude and Forbes, *J.*, 1951, 1755.
[36] Cronyn and Riesser, *J. Amer. Chem. Soc.*, 1953, **75**, 1664.
[37] Vavon and Apchié, *Bull. Soc. chim. France*, 1928, **43**, 667.
[38] Meerwein, *Annalen*, 1914, **405**, 129.
[39] Kon and Nutland, *J.*, 1926, 3101.

Fractional crystallisation (from ethanol–chloroform) of the 2:4-dinitrophenylhydrazone of fraction (1) yielded maroon laths, m. p. 222—223°, and crimson needles, m. p. 206—208° (decomp.), whose m. p.s were not depressed on admixture with the derivatives of authentic 2-*iso*propylidene-*cyclo*pentanone and 2-*iso*propyl*cyclo*pent-2-enone respectively. Repeated recrystallisation of the derivatives of fraction (5) gave the semicarbazone, m. p. 214—216°, and the 2 : 4-dinitrophenylhydrazone, m. p. 218—220° (decomp.), of 2-*iso*propylidene*cyclo*pentanone (identified by mixed m. p.). Hydrogenation of fractions (1) and (5) gave the same homogeneous product whose semicarbazone, m. p. 191—192°, and 2 : 4-dinitrophenylhydrazone, m. p. 154—155°, were not depressed in m. p. on admixture with derivatives of authentic 2-*iso*propyl-*cyclo*pentanone.

Cyclisation of 7-Methyloct-6-enoic Acid.—The ketonic material was combined and redistilled; its properties showed it to be a mixture of 2-*iso*propyl*cyclo*hex-2-enone (C) and 2-*iso*propylidene-*cyclo*hexanone (D). It had b. p. 95—98°/13 mm., n 1·4873, and $\lambda_{max.}$ 235—255 (broad) (log ε 1·74), $\lambda_{infl.}$ 3·5 mμ (log ε 1·81). Its heterogeneous semicarbazone, on repeated crystallisation from methanol, afforded plates, m. p. 193—194° not depressed on admixture with the derivative of (D); but its 2 : 4-dinitrophenylhydrazone, on crystallisation, afforded red needles, m. p. 186—192°, not depressed on admixture with the derivative of (C). 2-iso*Propyl*cyclo*hex*-2-*enone* (Found: C, 77·6; H, 10·4. $C_9H_{14}O$ requires C, 78·2; H, 10·2%), prepared from 2-iso-*propyl*cyclo*hexane*-1 : 3-*dione* [plates (from ethyl acetate), m. p. 153—154° (Found: C, 70·2; H, 9·1. $C_9H_{14}O_2$ requires C, 70·1; H, 9·25%)] *via* the enol *iso*butyl ether by the method of Born *et al.*,[24] had b. p. 92—92·5°/24 mm., n 1·4773, $\lambda_{max.}$ 235, 319 (log ε 3·82, 1·44), and gave a *semicarbazone*, prisms (from methanol), m. p. 166—167° (Found: C, 60·5; H, 8·7; N, 22·4. $C_{10}H_{17}ON_3$ requires C, 61·5; H, 8·8; N, 21·5%), and a 2 : 4-*dinitrophenylhydrazone*, red needles (from ethanol–chloroform), m. p. 190—191° (Found: C, 56·0; H, 5·6; N, 18·2. $C_{15}H_{18}O_4N_4$ requires C, 56·6; H, 5·7; N, 17·6%). 2-*iso*Propylidene*cyclo*hexanone [40] had b. p. 103·5—104·5°/24 mm. (lit., 120—125°/20 mm.), n 1·4922, $\lambda_{max.}$ 254, $\lambda_{infl.}$ 305 (log ε 3·80, 1·84), and gave a semicarbazone, plates (from methanol), m. p. 196—197° (lit., 184°) (Found: N, 21·3%), and a 2 : 4-dinitrophenylhydrazone, maroon plates (from ethanol–chloroform), m. p. 182—183° (lit., 162—163°) (Found: C, 56·4; H, 5·8%).

The 2 : 4-dinitrophenylhydrazone of the cyclisation product gave also a derivative (? of 2-*iso*butyl*cyclo*pent-2-enone), scarlet laths, m. p. 217—218° (Found: N, 17·9%).

Catalytic hydrogenation of the cyclisation product gave a mixture of saturated ketones from which the only isolable homogeneous derivative was a 2 : 4-dinitrophenylhydrazone (orange needles) whose m. p., 135—137°, was not depressed on admixture with the 2 : 4-dinitrophenylhydrazone, m. p. 137—140°, of 2-*iso*propyl*cyclo*hexanone.[41] Smith *et al.*[42] record m. p. 134—136°.

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Queen Mary College (University of London),
Mile End Road, E.1. [*Received, January 23rd,* 1958.]

[40] Mukerji, Gandhi, and Vig, *J. Indian Chem. Soc.*, 1956, **33**, 853.
[41] Kotz and Michels, *Annalen*, 1906, **350**, 213.
[42] Smith, Norton, and Ballard, *J. Amer. Chem. Soc.*, 1953, **75**, 3316.

XUM

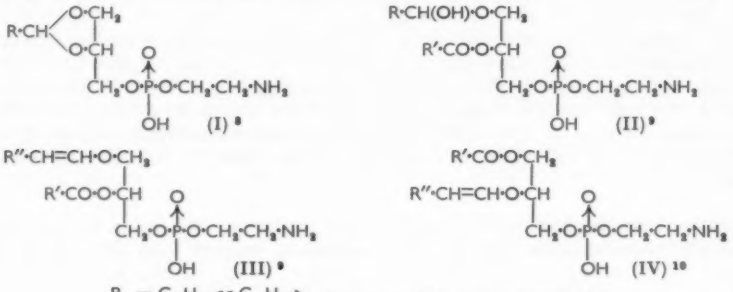
603. *The Synthesis of Cephalin (Phosphatidylethanolamine) and Batyl, Chimyl, Glycol, and Alkyl Analogues.*

By R. L. Baylis, T. H. Bevan, and T. Malkin.

Series of cephalins and batyl, chimyl, glycol, and alkyl analogues have been prepared by the silver salt–iodide interchange method described previously. The method produces high yields and avoids the formation of undesirable by-products. The relation of the batyl and the chimyl compounds to the structure of plasmalogens is indicated.

Cephalins have been synthesised by Rose,[1] Hunter, Roberts, and Kester,[2] Bevan and Malkin,[3] and Baer, Maurukas, and Russell,[4] by the action of phosphorus oxychloride or phenyl phosphorodichloridate on diglycerides, followed by further reaction with *N*-protected ethanolamine and subsequent removal of protecting groups. The above methods invariably give rise to unwanted bisphosphatidyl compounds which are troublesome to remove, and in order to avoid both this and the use of difficultly prepared, unstable 1 : 2-diglycerides, we have used the silver salt–iodide interchange method, described previously for the preparation of phosphatidic acids [5] and phosphatidylserine.[6] Glycerol 1-iodide 2 : 3-distearate [7] was allowed to react with silver 2-(benzyloxycarbonylamino)ethyl phenyl phosphate in boiling benzene in the dark, and the protecting groups were then removed by hydrogenolysis. This synthesis is superior to any that we have previously used, and the products melt sharply, without the sintering well below the melting point reported by other workers.[1, 4]

Batyl and chimyl analogues of cephalin are of interest in connection with the structure of plasmalogens, for which the following formulæ have been proposed:



R = $C_{17}H_{35}$ or $C_{15}H_{31}$ } and corresponding unsaturated radicals
R″ = $C_{16}H_{33}$ or $C_{14}H_{29}$ }
R′ = various fatty acid radicals

Compound (I) has been isolated from a natural source in a pure state [11] and its structure has been established by synthesis,[12] but it has been suggested that it is possibly an artefact, produced during extraction from the other above types.[10, 13]

[1] Rose, *J. Amer. Chem. Soc.*, 1947, **69**, 1384.
[2] Hunter, Roberts, and Kester, *ibid.*, 1948, **70**, 3244.
[3] Bevan and Malkin, *J.*, 1951, 2667.
[4] Baer, Maurukas, and Russell, *J. Amer. Chem. Soc.*, 1952, **74**, 152.
[5] Baylis, Bevan, and Malkin, *Chem. and Ind.*, 1955, 67.
[6] Bevan, Malkin, and Tiplady, *J.*, 1957, 3086.
[7] Fischer, *Ber.*, 1920, **53**, 1621; see also Bevan, Malkin, and Smith, *J.*, 1955, 1383.
[8] Feulgen and Bersen, *Z. physiol. Chem.*, 1939, **260**, 217.
[9] Klenk and Debuch, *ibid.*, 1954, **296**, 179.
[10] Rapport, Lerner, Alonzo, and Franzl, *J. Biol. Chem.*, 1957, **225**, 859.
[11] Thannhauser, Boncoddo, and Schmidt, *ibid.*, 1951, **188**, 417.
[12] Egerton and Malkin, *J.*, 1953, 2800; Malkin, Baylis, Bevan, and Webley, *Olii Grassi Colori*, 1956, **33**, 226. (Dr. Webley has now synthesised the optically active form by the Ag salt method.)
[13] Baer and Stancer, *J. Amer. Chem. Soc.*, 1953, **75**, 4510.

XUM

Compounds (II), (III), and (IV) have not so far been isolated in a pure state, but Klenk and Debuch [9] found that a reasonably pure specimen of plasmalogen on catalytic reduction with Raney nickel yielded a mixture of batyl and chimyl analogues of cephalin. We are not aware of any evidence concerning the catalytic reduction of hemiacetals of type (II), but there is little doubt that the substituted vinyl ethers (III) and (IV) would be reduced to the batyl (chimyl) derivatives and their isomers respectively.

We have therefore synthesised a number of batyl and chimyl analogues of cephalin for comparison with the naturally derived products. For this we employed the method described above, using acylated batyl (chimyl) iodides and xylene instead of benzene. These compounds are practically indistinguishable from the true cephalins of the same chain lengths in physical properties (solubility, m. p., *X*-ray data), and it seems to us not at all unlikely that they may occur naturally, but have hitherto escaped detection because of this remarkably close similarity. The recent isolation of a natural long-chain ether, glycerol lysophosphatide, by Carter *et al.*[14] supports this view.

Acylglycol cephalin analogues have not been prepared previously, but the corresponding glycol lecithins were synthesised by Baer,[15] who showed that they were intermediate in properties between lecithin and lysolecithin and had hæmolytic properties. We have prepared a series for general comparisons by the above silver salt method and find no unusual features. The group exhibits the expected m. p., solubility, and *X*-ray relations.

The only previous synthesis of an alkyl analogue of cephalin is due to Christensen [16] who prepared 2-aminoethylcetyl phosphate in low yield starting from ethylene chlorohydrin, phosphoryl chloride, and cetyl alcohol. The silver salt method gives high yields of these compounds, and we have prepared a series from C_{12}, C_{14}, C_{16}, and C_{18} *n*-alkyl iodides.

The solubility of the above compounds in organic solvents diminishes sharply as the number and length of the hydrocarbon chains decrease. All are white and crystalline. Alkyl and glycol cephalins, from glacial acetic acid, and batyl and chimyl cephalins, from chloroform, crystallise in characteristic spherulitic forms, previously reported for cephalins.[3]

The m. p. data given in Table 1 are of interest because of the fall in m. p. with increasing molecular weight. This unusual property is a feature of high-melting long-chain compounds, which with increasing length of chain, approach the m. p. limit for hydrocarbon chains (*ca.* 125°) [17] (cf., *e.g.*, even-membered dibasic acids and fatty acid amides).

TABLE 1. *M.p.s of cephalins and cephalin analogues.*

Carbon content of fatty acids or alkyl group	Cephalin [3]	Cephalin analogues			
		Batyl	Chimyl	Alkyl	Glycol
C_{18}	196°	195°	198°	239°	216°
C_{16}	198	197	201	242	218
C_{14}	207	200	205	245	222
C_{12}	210	203	207	249	224

X-Ray Examination.—This was carried out as described in earlier papers.[3,18] Long spacings of batyl and chimyl cephalins were difficult to determine, but no difficulty was experienced with the short spacings which are given (Table 2) with those of cephalin for comparison. The data are the averages of those for eight different batyl and chimyl derivatives (lauroyl, myristoyl, palmitoyl, and stearoyl) and the averages of four different cephalins.[3] No individual spacing differs from the average by more than 0·04 Å.

The above long spacings plotted against the number of carbon atoms in the acyl groups give a straight line with an intercept at C = 0 of 26 Å. The data correspond with an arrangement of double molecules lying vertically between the reflecting planes.

For alkyl cephalins (Table 4), the long spacings and the intensities of the side spacings

[14] Carter, Galanos, Gigg, Law, Teishi Nakayama, Smith, and Weber, *Fed. Proc.*, 1957, **16**, 819.
[15] Baer, *J. Amer. Chem. Soc.*, 1953, **75**, 5533.
[16] Christensen, *J. Biol. Chem.*, 1940, **135**, 399.
[17] Garner and King, *J.*, 1936, 1368.
[18] "Progress in the Chemistry of Fats," Vol. 1, p. 1, Pergamon Press Ltd., London, 1952.

show a marked discontinuity in structure between C_{14} and C_{16}. If the long spacings are plotted against the number of carbon atoms in the alkyl group, they fall on parallel lines intercepting the axes at C = 0 at 16·6 Å (C_{16}, C_{18}) and 12·4 Å (C_{12}, C_{14}). The data at

TABLE 2. *Short spacings* (Å)

Batyl and chimyl cephalins	5·91 w	4·86 w	4·14 vs	3·83 m	3·56 w
Cephalin	5·92 w	4·93 w	4·18 vs	3·86 m	3·60 w

Intensity: m = moderate; vs = very strong; w = weak.

TABLE 3. *Acylglycol cephalins.*

Carbon atoms in acyl group	Long spacing (Å)	Short spacings (Å)				
12	56·9	5·8 m	5·3 m	4·7 m	4·0 s	3·8 s
14	61·6	5·7 m	5·2 m	4·6 m	4·0 s	3·8 s
16	66·9	5·8 m	5·2 m	4·7 m	4·0 s	3·8 s
18	72·0	5·8 m	5·2 m	4·6 m	4·0 s	3·8 s

TABLE 4. *Alkyl cephalins (alkyl β-aminoethyl phosphates).*

Carbon atoms in alkyl group	Long spacing (Å)	Short spacings (Å)				
12	24·7	5·8 w	5·4 w	4·6 m	4·0 s	3·8 s
14	26·7	5·8 w	5·4 w	4·6 m	3·9 s	3·8 s
16	32·6	5·8 w	5·4 w	4·6 vs	4·0 s	3·9 s
18	34·7	5·8 w	5·4 w	4·6 vs	3·9 s	3·8 s

present available do not distinguish between an arrangement of single molecules tilted at angles of 55° 40′ and one of double molecules tilted at an angle of 24° 20′ across the reflecting planes.

EXPERIMENTAL

Silver 2-(Benzyloxycarbonylamino)ethyl Phenyl Phosphate.—*N*-Benzyloxycarbonylethanolamine (50·4 g.) in dry chloroform (*ca.* 300 c.c.) was added with stirring and ice-cooling to phenyl phosphorodichloridate (54·7 g.) in dry chloroform (50 c.c.) and dry quinoline (35 g.) during 8 hr. After being kept overnight at room temperature, the chloroform was removed under reduced pressure at <40°, and pyridine (20 g.) was then added, followed by water (10 c.c.) dropwise, with stirring and cooling. After 24 hr. at room temperature, water (150 c.c.) was added, followed by three equivalents of potassium carbonate (57·2 g.). The aqueous solution was extracted with ether (3 × 200 c.c.) to remove, *inter alia*, the bisphosphoryl compound and was finally taken to dryness under reduced pressure at <40°. The residue was extracted with ethanol until it no longer gave a positive nitrogen test, and on evaporation of the combined extracts (reduced pressure, <40°), there remained the potassium salt of the acid (56—57 g.) in the form of a viscous oil. This was taken up in water (50 c.c.), and the solution was made just acid to litmus with 2N-nitric acid. Silver nitrate (28 g. in 28 c.c. of water) was then added with vigorous stirring, and after storage overnight the precipitated *silver salt* was filtered off, washed successively with water and ethanol, and dried in *vacuo* over concentrated sulphuric acid for several days (yield 52 g.) (Found: Ag, 23·6. $C_{16}H_{17}O_6NPAg$ requires Ag, 23·5%).

In the following silver salt interchange reactions, it is important that the salt and all reagents be thoroughly dry.

1 : 2-*Distearoylphosphatidyl Ethanolamine.*—Glycerol 1-iodide 2 : 3-distearate (1·84 g., 0·0025 mole) in dry benzene (50 c.c.) was refluxed with the above silver salt (1·37 g., 0·003 mole) in the dark with stirring, for 3 hr. After cooling and filtration (Filtercel) the solvent was removed under reduced pressure at <40° and the residue was taken up in ether. The ethereal solution was treated with aqueous sodium hydrogen carbonate solution, to remove traces of acidic material which is usually produced in this reaction, and after being washed with water and dried the solvent was removed under reduced pressure and the residue crystallised twice from light petroleum (b. p. 40—60°). It (2 g., 83%) had m. p. 47—48° (Found: C, 68·7; H, 9·5; N, 1·5; P, 3·0. Calc. for $C_{55}H_{92}O_{10}NP$: C, 68·9; H, 9·7; N, 1·5; P, 3·2%).

Hydrogenolysis. The above distearoyl compound (0·9 g.) was hydrogenated in glacial acetic acid (30 c.c.) at 1 atm. in the presence of 1 : 1 palladium black–palladium oxide (Adams)

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(1·0 g.) until hydrogen uptake ceased. After removal of excess of hydrogen, chloroform was added to dissolve precipitated product, and the catalyst was filtered off and washed with chloroform. The filtrate was evaporated to dryness under reduced pressure and final traces of impurities were removed from the residue by extraction with boiling ether (3 × 100 c.c.). Final crystallisation from ethanol gave material (0·6 g.) of m. p. 198° (Found: C, 65·6; H, 10·7; N, 2·0; P, 4·0. Calc. for $C_{41}H_{82}O_8NP$: C, 65·9; H, 11·0; N, 1·9; P, 4·2%). This compound was identical with that previously prepared.[3]

Dipalmitoyl and dimyristoyl cephalin were prepared similarly.

Batyl and Chimyl Alcohol.[19]—These were prepared by the method used by Howe and Malkin [20] for the preparation of glycerol 1-benzyl ether.

1:2-O-iso*Propylideneglycerol* 1-*octadecyl ether*. Sodium (4·4 g., 0·19 mole) was granulated under boiling xylene and 1 : 2-*O*-*iso*propylideneglycerol [21] (29 g., 0·22 mole) was added dropwise to the stirred, cooled mixture. After the initial reaction had subsided, the reaction was completed by refluxing and stirring. Octadecyl iodide (72·2 g., 0·19 mole) in dry xylene (150 c.c.) was then added to the gently refluxing, stirred mixture during 15 min. and heating and stirring were continued for a further 6 hr. After cooling, the precipitated sodium iodide was removed and washed with chloroform, and the solvent was removed under reduced pressure. The residual viscous oil was dissolved in ether, washed, and dried (Na_2SO_4). After removal of solvents the residue was distilled *in vacuo* (b. p. 210—215°/1 mm., m. p. 32—33°; 49·6 g., 68%) (Found: C, 74·8; H, 12·2. Calc. for $C_{24}H_{48}O_3$: C, 75·0; H, 12·5%).

Batyl alcohol. The above *iso*propylidene compound (49·6 g.) was heated on a water-bath with 10% aqueous acetic acid (425 c.c.) with frequent shaking until the original emulsion had disappeared (*ca.* 2 hr.). After cooling, ice-cold water was slowly added to the solution until precipitation was complete. The product was filtered off, through a filter with a large area, and washed with water. The product was then heated for 0·5 hr. with excess of dilute sodium hydroxide solution on a water-bath and after cooling was filtered, washed free from alkali with water, and dried in *vacuo*. On crystallising from acetone, 40·5 g. (90%) of pure batyl alcohol were obtained, having m. p. 71—72° (Found: C, 73·3; H, 12·9. Calc. for $C_{21}H_{44}O_3$: C, 73·3; H, 12·8%).

Chimyl alcohol. 1 : 2-*O*-*iso*Propylideneglycerol (30·3 g.), sodium (4·6 g.), and hexadecyl iodide (70·4 g.) yielded 50·7 g. (71%) of the *iso*propylideneglycerol ether, b. p. 173—178°/2 mm. (Found: C, 74·3; H, 12·1. Calc. for $C_{22}H_{44}O_3$: C, 74·2; H, 12·4%).

This (50·7 g.), on hydrolysis with 10% aqueous acetic acid, yielded 41·0 g. (91%) of chimyl alcohol, m. p. 62—63° (Found: C, 72·4; H, 12·5. Calc. for $C_{19}H_{40}O_3$: C, 72·2; H, 12·7%).

Batyl and Chimyl 1-*Iodide*.—These were prepared by the interaction of the toluene-*p*-sulphonates of the alcohols and sodium iodide in dry acetone. We had considerable difficulty in acylating the alcohols. Neither toluene-*p*-sulphonyl chloride nor the bromide reacts with the alcohols in pyridine or in a variety of solvents with pyridine * at varying temperatures, but we finally obtained the sulphonyl derivatives as follows. Potassium (2·0 g., 0·053 mole) was granulated under dry xylene (250 c.c.) at 100°, by vigorous stirring, then cooled to 40°. Batyl alcohol (18·2 g., 0·053 mole) was added in bulk with vigorous stirring and after the initial reaction had subsided the mixture was refluxed and stirred until all the potassium had reacted. The mixture was cooled to room temperature, becoming gelatinous, and toluene-*p*-sulphonyl chloride (10·1 g., 0·053 mole) was added to the stirred mixture. Reaction began at once with a slight rise in temperature which cleared the gelatinous precipitate, and shortly afterwards potassium chloride began to separate. Stirring at room temperature was continued for 3 hr. and at 60° for 30 min. The precipitated potassium salt was removed by filtration and washed with chloroform, and after removal of the solvent from the filtrate and washings, the resultant viscous oil was dissolved in pyridine (20 c.c.) and the solution was poured into ice-cold water (200 c.c.) to remove any excess of toluene-*p*-sulphonyl chloride.

The oil which separated was extracted with ether, and the solution was filtered to remove unchanged batyl alcohol and washed successively with N-hydrochloric acid, saturated sodium

* We have since found that these alcohols are acylated satisfactorily in concentrated solutions in pyridine.

[19] See Stegerhoek and Verkade, *Rec. Trav. chim.*, 1956, **75**, 143, for an alternative method of preparation.

[20] Howe and Malkin, *J.*, 1951, 2663.

[21] Malkin and Shurbagy, *J.*, 1936, 1634.

hydrogen carbonate solution, and water. After drying (Na_2SO_4) and removal of solvent under reduced pressure, there remained 13·2 g. (40%) of a viscous oil. This proved difficult to crystallise, but after its dissolution in light petroleum (b. p. 40—60°) and storage for several days 3·5 g. of *batyl toluene*-p-*sulphonate* crystallised, having m. p. 59—61°, raised to 61—62° by further crystallisation from the same solvent (Found: C, 67·8; H, 10·0. $C_{28}H_{50}O_5S$ requires C, 67·5; H, 10·0%). Evaporation of the mother-liquor and drying in *vacuo* at 40° yielded 9·5 g. of viscous oil (A). This slightly impure product could be satisfactorily carried through to the acylated batyl iodide, which lends itself better to purification.

Batyl 1-*iodide*. Batyl toluene-*p*-sulphonate (3 g.) in dry acetone (100 c.c.) containing sodium iodide (3 g.; 3 times theoretical amount) was refluxed for 24 hr. After cooling, the precipitated sodium toluene-*p*-sulphonate was filtered off, washed with acetone, and dried (1·1 g., 100%) and the filtrate and washings were evaporated to dryness under reduced pressure. The iodide was extracted from the residue with ether, and the ethereal solution was washed with 10% sodium thiosulphate solution and with water, and dried. Removal of ether under reduced pressure yielded a white solid (2·4 g., 90%), m. p. 41—43°. No suitable solvent could be found for the crystallisation of this compound. It is very soluble in methanol and ethanol, acetone, benzene, hexane, and light petroleum. Crystallisation did not occur from these during some days at 0°. Both the m. p. range and the analytical data suggest that the above product contained a little unchanged ester.

The viscous oil (A) (9·5 g.) was treated as above with sodium iodide (8·4 g.) in acetone, 3·4 g. of sodium toluene-*p*-sulphonate being precipitated (theor. 3·7 g.). Working up as above gave 7·0 g. of a viscous oil (80%).

[Added, June 23rd, 1958.] Batyl alcohol (3·44 g.) was added to a mixture of toluene-*p*-sulphonyl chloride (2·5 g.) and pyridine (5 c.c.) with shaking and slight warming until all the batyl alcohol had dissolved. Pyridine hydrochloride soon began to separate and after storage overnight water was added and the product was extracted with ether. After treatment of the ethereal solution as described previously, there remained a solid which after two crystallisations from light petroleum (b. p. 40—60°) yielded 2·8 g. of batyl toluene-*p*-sulphonate, m. p. 61—62°.

Batyl 1-*iodide* 2-*stearate*. Batyl 1-iodide (2 g., 0·0044 mole) was refluxed with stearoyl chloride (1·33 g., 0·0044 mole) in dry benzene (50 c.c.) containing dry pyridine (3 c.c.) for 6 hr. The precipitated pyridine hydrochloride was then removed and the benzene distilled off under reduced pressure. The viscous residue was dissolved in ether, and the ethereal solution was washed successively with N-hydrochloric acid, saturated sodium hydrogen carbonate solution, 10% sodium thiosulphate solution, and water, and dried (Na_2SO_4). After removal of solvent, the residue was crystallised from ethanol, and after recrystallisation the product still melted over a range of 36—41°. The impurity was found to be stearic acid, and this was removed by passing a chloroform solution of the product a few times down a column of Amberlite resin IRA-400(OH). Removal of chloroform and crystallisation from ethanol yielded colourless *diester* (2·0 g., 65%), m. p. 37—38° (Found: C, 64·8; H, 10·5. $C_{39}H_{77}O_3I$ requires C, 65·0; H, 10·7%). The above slightly impure iodide (7 g.; viscous oil) was acylated in a similar manner with stearoyl chloride (4·6 g.) to yield 6·6 g. (61·0%) of pure product, m. p. 37—38°.

Similarly batyl 1-iodide (3·6 g.) and palmitoyl chloride (2·2 g.) gave *batyl* 1-*iodide* 2-*palmitate* (3·5 g., 65%), m. p. 31—32° (Found: C, 64·0; H, 10·3. $C_{37}H_{73}O_3I$ requires C, 64·6; H, 10·55%).

Batyl 1-iodide (5·9 g.) and myristoyl chloride (3·2 g.) gave batyl 1-iodide 2-myristate (5·3 g., 61%); batyl 1-iodide (4·5 g.) and lauroyl chloride (2·2 g.) gave the 2-laurate (4 g., 63%).

The myristoyl and lauroyl compounds were liquids at room temperature and could not readily be purified by crystallisation. They were purified to some extent by two extractions with warm methanol, the latter being removed by decantation. A chloroform solution of the product was then passed down a resin column as already described.

2-*Acyl Chimyl* 1-*Iodides*.—The chimyl iodide and acyl iodides were made as described for the batyl compounds.

Chimyl 1-*toluene*-p-*sulphonate*. Chimyl alcohol (28·6 g.), potassium (3·5 g.), and toluene-*p*-sulphonyl chloride (17·1 g.) yielded 5·3 g. of crystalline *product* [from light petroleum (b. p. 40—60°)], m. p. 53—54° (Found: C, 66·6; H, 9·8. $C_{26}H_{46}O_5S$ requires C, 66·4; H, 9·8%). 20·8 g. of slightly impure product were also obtained as a viscous oil.

Chimyl 1-*iodide*. The above solid toluene-*p*-sulphonyl compound (5·0 g.) was refluxed with sodium iodide (4·8 g.) in dry acetone (150 c.c.) for 24 hr. Sodium toluene-*p*-sulphonate (2·0 g.;

theor. 2·06 g.) was precipitated. After working up as for batyl iodide, a white solid (4·2 g., 93%) was obtained (m. p. 35—37°). No suitable solvent could be found for crystallisation and analysis indicated the presence of a small amount of sulphonyl compound.

The viscous oil (20·8 g.) from the previous experiment was treated with sodium iodide (20·0 g.) as above; 7·5 g. of sodium toluene-*p*-sulphonate were precipitated (88% yield; theor. 8·6 g.). After working up as previously described, 16·2 g. (86%) of viscous oil were obtained.

Chimyl 1-iodide (4·1 g.) and stearoyl chloride (2·9 g.) gave *chimyl 1-iodide 2-stearate* (5·1 g., 77%), m. p. 32—33° (Found: C, 63·9; H, 10·4. $C_{37}H_{73}O_3I$ requires C, 64·2; H, 10·6%).

Chimyl 1-iodide (5·3 g.) and palmitoyl chloride gave *chimyl 1-iodide 2-palmitate* (5·5 g., 66%), m p. 25—26° (Found: C, 63·0; H, 10·2. $C_{35}H_{69}O_3I$ requires C, 63·3; H, 10·4%).

Chimyl 1-iodide (5·3 g.) and myristoyl chloride (3·0 g.) gave chimyl 1-iodide 2-myristate (5 6 g., 70%); chimyl 1-iodide (5·1 g.) and lauroyl chloride (2·6 g.) gave chimyl 1-iodide 2-laurate (5·4 g., 74%). The myristoyl and lauroyl compounds were liquid and were purified in a similar manner to the batyl compounds.

2-Aminoethyl 2-O-*Stearoylbatyl Phosphate* (*Stearoyl Batyl Cephalin*).—Batyl 1-iodide 2-stearate (6·7 g., 0·0093 mole) in dry xylene (30 c.c.) was added to a solution of silver 2-(benzyloxycarbonylamino)ethyl phenyl phosphate (4·6 g., 0·01 mole) in boiling xylene (200 c.c.) in the dark with vigorous stirring. Silver iodide was precipitated almost immediately, and refluxing and stirring were continued for 30 min. After cooling to room temperature, the silver salt was filtered off (Filtercel) and washed with benzene, and the filtrate was evaporated under reduced pressure at $<50°$. The residue was taken up in ether, treated twice with saturated sodium hydrogen carbonate solution, washed with water, and dried (Na_2SO_4). After removal of ether under reduced pressure, there remained 7·7 g. of low-melting solid. This was hydrogenolysed in glacial acetic acid (150 c.c.) and chloroform (50 c.c.) at slightly >1 atm. in the presence of 2 g. of a 1 : 1 mixture of palladium black–platinum oxide (Adams). When the uptake of hydrogen had ceased, the catalyst was removed and washed with chloroform, and the solvents were removed from the filtrate under reduced pressure at $<40°$. Final traces of acetic acid were removed by azeotropic evaporation with benzene. The residue was extracted three times with ether, and crystallised from chloroform–ethanol, giving the *phosphate* (2·9 g., 48%), m. p. 195° (decomp.) (Found: C, 67·0; H, 11·4; N, 2·1; P, 4·1. $C_{41}H_{84}O_7NP$ requires C, 67·1; H, 11·5; N, 1·9; P, 4·2%). The overall yield based on iodo-compound is 42%.

The remaining batyl analogues were made similarly. The *palmitoyl derivative* was crystallised from chloroform–ethanol, and the *myristoyl* and *lauroyl derivatives* from ethanol (see below). Yields were 38—41%. M. p.s are in Table 1.

Palmitoyl (Found: C, 66·2; H, 11·3; N, 2·1; P, 4·3. $C_{39}H_{80}O_7NP$ requires C, 66·4; H, 11·3; N, 2·0; P, 4·4%).

Myristoyl (Found: C, 65·5; H, 11·1; N, 2·2; P, 4·7. $C_{37}H_{76}O_7NP$ requires C, 65·6; H, 11·2; N, 2·1; P, 4·6%).

Lauroyl (Found: C, 64·6; H, 11·1; N, 2·1; P, 4·8. $C_{35}H_{72}O_7NP$ requires C, 64·7; H, 11·1; N, 2·2; P, 4·8%).

The corresponding *acyl chimyl cephalins* (see below) were made similarly except that the time of refluxing in xylene was reduced from 30 min. to 10 min. with a considerable improvement in yield (50—58%). Stearoyl and palmitoyl derivatives were crystallised from chloroform–ethanol, and myristoyl and lauroyl derivatives from ethanol. M. p.s are in Table 1.

Stearoyl (Found: C, 66·0; H, 11·4; N, 2·0; P, 4·5. $C_{39}H_{80}O_7NP$ requires C, 66·4; H, 11·3; N, 2·0; P, 4·4%).

Palmitoyl (Found: C, 65·4; H, 11·0; N, 2·0; P, 4·7. $C_{37}H_{76}O_7NP$ requires C, 65·6; H, 11·2; N, 2·1; P, 4·6%).

Myristoyl (Found: C, 64·4; H, 11·1; N, 2·3; P, 4·5. $C_{35}H_{72}O_7NP$ requires C, 64·7; H, 11·1; N, 2·3; P, 4·8%).

Lauroyl (Found: C, 63·6; H, 11·1; N, 2·3; P, 5·2. $C_{33}H_{68}O_7NP$ requires C, 63·8; N, 11·0; N, 2·3; N, 5·0%).

Glycol and alkyl cephalins (see below) were made as described for cephalins, by using 2-iodoethyl fatty esters [22] and alkyl iodides respectively. Yields were of the order of 75—85%. M. p.s are in Table 1.

Glycol cephalins: *stearoyl* (Found: C, 58·4; H, 10·3; N, 3·3; P, 6·8. $C_{22}H_{46}O_6NP$ requires C, 58·5; H, 10·2; N, 3·1; P, 6·9%); *palmitoyl* (Found: C, 56·5; H, 10·0; N, 3·3; P, 7·0.

[22] Bevan, Malkin, and Smith, *J.*, 1955, 1043.

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$C_{20}H_{42}O_6NP$ requires C, 56·7; H, 10·0; N, 3·3; P, 7·3%); *myristoyl* (Found: C, 54·6; H, 9·7; N, 3·5; P, 7·9. $C_{18}H_{38}O_6NP$ requires C, 54·7; H, 9·6; N, 3·5; P, 7·9%); *lauroyl* (Found: C, 52·3; H, 9·3; N, 3·9; P, 8·2. $C_{16}H_{34}O_6NP$ requires C, 52·3; H, 9·3; N, 3·8; P, 8·4%).

2-Aminoethyl phosphates: *octadecyl* (Found: C, 61·2; H, 11·1; N, 3·9; P, 7·9. $C_{20}H_{44}O_4NP$ requires C, 61·1; H, 11·2; N, 3·6; P, 7·9%); hexadecyl (Found: C, 59·0; H, 11·2; N, 3·9; P, 8·5. Calc. for $C_{18}H_{40}O_4NP$: C, 59·2; H, 11·0; N, 3·8; P, 8·5%); *tetradecyl* (Found: C, 56·9; H, 10·8; N, 4·3; P, 9·4. $C_{16}H_{36}O_4NP$ requires C, 57·0; H, 10·7; N, 4·2; P, 9·2%); *dodecyl* (Found: C, 54·4; H, 10·3; N, 4·6; P, 10·0. $C_{14}H_{32}O_4NP$ requires C, 54·4; H, 10·4; N, 4·5; P, 10·0%).

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THE UNIVERSITY, BRISTOL. [*Received, March 17th,* 1958.]

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604. *Studies on Phosphorylation. Part XVII.* The Hydrolysis of Methyl* 3-(OO-*Dimethylphosphoryloxy*)*but*-2-*enoate.*

By E. Y. SPENCER, SIR ALEXANDER TODD, and R. F. WEBB.

Hydrolysis of the esters (Ia and b) has been examined; the results indicate that partial hydrolysis products are unlikely to account for their biological activity. Preliminary data on hydrolysis under oxidising conditions suggest that such processes may be involved in their activation *in vivo*.

RECENT investigation [1] in these laboratories has had as its ultimate aim the development of reagents for phosphorylation in aqueous media. In a broad sense many organophosphorus insecticides may be considered as reagents of this type since the mode of inhibition of certain hydrolases, *e.g.*, chymotrypsin,[2] has been demonstrated to involve phosphorylation of the enzyme. It was considered that a further insight into phosphorylation processes might be obtained by a study of certain of these organophosphorus compounds *in vivo* and *in vitro* and, in particular, we wished to investigate those compounds which show low reactivity both in hydrolysis and towards enzymes *in vitro* but are rapidly metabolised and are highly toxic *in vivo*. This behaviour, typical of certain insecticides, is usually attributed to the conversion of the compounds, in the plant, insect, or mammal into unstable and active phosphorylating agents,[3] a typical example being the activation of octamethylpyrophosphoramide (" Schradan ") by oxidation.[4] The present paper deals with the hydrolysis and derivatives of a recently reported [5] systemic insecticide of this type methyl 3-(*OO*-dimethylphosphoryloxy)but-2-enoate (I) (" Phosdrin ") and attempts to elucidate the nature of its activation. Two possible modes of activation appeared possible, one involving oxidation to a ketal derivative (II) and the other a partial hydrolysis, it being expected that the *cis*-derivative (Ia; R, R′, R″ = Me) might display the high reactivity of the similarly constituted salicylyl and *o*-carboxynaphthyl phosphate.[6] The instability of " Phosdrin " and especially of the *cis*-isomer in the plant has been demonstrated by Casida *et al.*[7]

" Phosdrin " was readily separated into two geometrical isomers (Ia and b) by countercurrent distribution in ether–water, the separation being followed by ultraviolet

* Part XVI, *J.*, 1958, 528.

[1] Clark, Kirby, and Todd, *J.*, 1957, 1497; Khorana and Todd, *J.*, 1953, 2257.
[2] Schaffer, May, and Summerson, *J. Biol. Chem.*, 1953, **202**, 69; 1954, **206**, 201; Aldridge, *Ann. Reports*, 1956, **53**, 294.
[3] O'Brien and Spencer, *Ann. Rev. Entomology*, 1957, **2**, 261.
[4] Spencer, *Chem. Soc. Special Publ.*, No. 8, 1957, p. 171.
[5] Stiles, U.S.P., 2,685,552/1954.
[6] Chandley, Gindler, and Sobotka, *J. Amer. Chem. Soc.*, 1952, **74**, 4347; Chandley and Gindler, *ibid.*, 1953, **75**, 4035.
[7] Casida, Gatterdam, Getzin, and Chapman, *J. Agric. Food Chem.*, 1956, **4**, 722.

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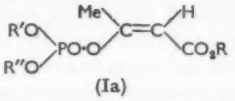
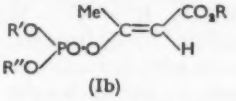
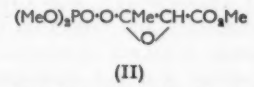
absorption measurements at 218 mμ; the separated components were distinguished by refractive index and by characteristic infrared absorption, the *cis*-isomer showing a strong absorption at 897 and the *trans*- at 913 cm.$^{-1}$. The isomers were separately hydrolysed



(Ia)



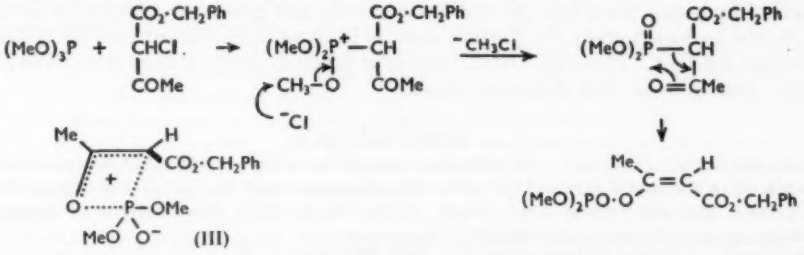
(Ib)



(II)

at pH 11 and 30°; after 24 hours, when hydrolysis was virtually complete, the *trans*-isomer had consumed 2·4 mols. of alkali and the *cis* 1·9 mols., although initially the rate of alkali uptake was approximately the same. Paper chromatography of the hydrolysis products indicated that the *trans*-isomer gave dimethyl hydrogen phosphate together with a trace of a component subsequently identified as methyl *trans*- 3-(*O*-methylphosphoryloxy)but-2-enoate (Ib; R = R′ = Me, R″ = H). The *cis*-isomer gave a more complex mixture containing dimethyl hydrogen phosphate and appreciable amounts of two other components identified as (Ia; R = H, R′ = R″ = Me; and R = R′ = Me, R″ = H); in both cases acetone and a trace of methyl dihydrogen phosphate were also produced. Thus the *trans*-isomer reacts almost exclusively by attack of hydroxide ion on phosphorus, the absence of product (Ib; R = H, R′ = R″ = Me) in spite of its expected stability indicating that this probably occurs more rapidly than hydrolysis at the carboxylic ester. The *cis*-isomer (Ia; R = R′ = R″ = Me) however is hydrolysed at the phosphoric and (more rapidly) at the carboxylic ester groups and further, whilst both isomers are hydrolysed at the phosphate ester group by predominant fission of the enol-phosphate linkage, the *cis*-form gives a higher proportion of P–O–CH_3 cleavage. The results reflect the ability of the *trans*-olefinic system to transmit the inductive effect of the methoxycarbonyl group and the steric effect in the *cis*-isomer, and both effects may be compared with those operating in *cis*- and *trans*-αβ-unsaturated acids where they determine the differing acid strengths.[8]

The greater reactivity of the *cis*-form of " Phosdrin " on hydrolysis at the methoxycarbonyl group was also demonstrated by a partial hydrolysis of the mixed isomers (*cis* 60%, *trans* 40%) in M-sodium carbonate at 30°, the recovered " Phosdrin " being shown to be predominantly the *trans*-form, whilst fractional acidification of the hydrolysate afforded *cis*-3-(*OO*-dimethylphosphoryloxy)but-2-enoic acid (Ia; R = H, R′ = R″ = Me), identified by paper chromatography and conversion into the ester (Ia; R = R′ = R″ = Me) by diazomethane. The pure *cis*-carboxylic acid (Ia; R = H, R′ = R″ = Me) was obtained by the hydrogenolysis of benzyl *cis*-3-(*OO*-dimethylphosphoryloxy)but-2-enoate (Ia; R = CH_2Ph, R′ = R″ = Me) prepared by treatment of benzyl α-chloroacetoacetate with trimethyl phosphite. It is of interest that similar treatment of methyl α-chloroacetoacetate with trimethyl phosphite gives a mixture of *cis*- and *trans*-products.[5] The steric control of the reaction with the benzyl ester could be explained by considering the formation of the " Phosdrin " derivative to involve an Arbusov reaction [9] between the chloro-ester and the trimethyl phosphite with a subsequent phosphonate rearrangement:



(III)

[8] Ingold, " Structure and Mechanism in Organic Chemistry," Bell and Co., 1953, Chapter 13, p. 745; Dippy, *Chem. Rev.*, 1939, **25**, 187.

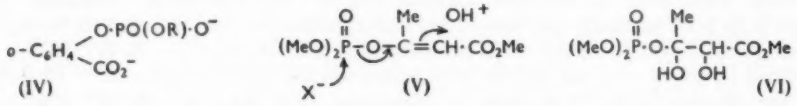
[9] Arbusov, *J. Soc. Phys. Chim. Russ.*, 1906, **38**, 687; Kosolapoff, *J. Amer. Chem. Soc.*, 1944, **66**, 109.

eclipsing of the methyl and the benzyloxycarbonyl group in the formation of the transition state (III) of the phosphonate–phosphate rearrangement is at a minimum for production of the *cis*-isomer. An attempt to determine the configuration of the double bond in the allyl analogue (I; R = CH_2·CH:CH_2, R′ = R″ = Me), prepared from allyl α-chloroacetoacetate and trimethyl phosphite, by hydrogenolysis and esterification with diazomethane could not be made since the allyl derivative underwent reduction to the *n*-propyl derivative and not hydrogenolysis to the carboxylic acid; however, counter-current distribution of the allyl ester indicated that a mixture had been formed.

The *cis*-acid (Ia; R = H, R′ = R″ = Me) was only slowly hydrolysed under mild conditions, having a half-life of 50 hours at pH 11 and 30°, and did not show any maximum in the rate of hydrolysis at intermediate pH values as do salicylyl and α-carboxynaphthylphosphate at pH 5—6. Our results parallel those of Montgomery, Turnbull, and Wilson [10] who were unable to demonstrate easy hydrolysis of steroid esters of salicylyl phosphate (IV; R = steroid residue) under conditions where the dianion (IV; R = H) undergoes rapid hydrolysis to salicylic acid and inorganic phosphate.

A similar slow hydrolysis was shown by methyl *cis*- and *trans*-3-(*O*-methylphosphoryloxy)but-2-enoate (I; R = R′ = Me, R″ = H) which were prepared by anionic demethylation of the corresponding " Phosdrin " derivatives by sodium iodide in acetone.[11] From the resistance to further hydrolysis shown by the partially hydrolysed derivatives of " Phosdrin " it appears that none of these intermediates can be considered as the " active component " in biological reactions of the compound and, although it has been pointed out [12] that the rate of attack by a nucleophilic site in an enzyme does not necessarily parallel that of hydroxide ion, we conclude that some other activation process or processes must be operating *in vivo*.

We therefore turned to an oxidative step as a possible activation process, it being considered that an activation *in vivo* might arise by the process (V), leading to the production of a phosphorylated enzyme and hydroxyacetone. In aqueous pertungstic acid [13] (pH 5·5, 70°) " Phosdrin " was rapidly hydrolysed to dimethyl hydrogen phosphate.



A solution of sodium hypobromite (pH 9·5, 20°) had a similar effect; in the absence of bromine at pH 9·5, 20° " Phosdrin " was only very slowly hydrolysed. These reactions may be interpreted on the basis of attack on the phosphate ester initiated by attack of OH^+ or Br^+ on the olefinic bonds and provide a possible mechanism of oxidative phosphorylation for esterase inhibition by the insecticide. An alternative explanation of the above hydrolysis involving formation and decomposition of a semi-ketal derivative (VI), whilst possible, is considered less likely since it should lead also to products other than dimethyl hydrogen phosphate formed by intermolecular phosphoryl migration involving the vicinal hydroxyl group.[14] Further work is in hand with isolated enzyme systems to determine whether " Phosdrin " or its hydrolysis products are metabolised by an oxidative process analogous to that discussed above.

Experimental

cis- *and* trans-" *Phosdrin*."—A redistilled commercial sample (12·56 g.) of the mixed isomers was placed in the first 5 tubes of an automatic counter-current battery of 100 tubes with 20·5 c.c. phases, and the system ether–water. After 95 transfers the contents of appropriate

[10] Montgomery, Turnbull, and Wilson, *J.*, 1956, 4603.
[11] Zervas and Dilaris, *J. Amer. Chem. Soc.*, 1955, **77**, 5354.
[12] Aldridge, *Ann. Reports*, 1956, **53**, 297.
[13] Mugdan and Young, *J.*, 1949, 2988.
[14] Brown, Magrath, and Todd, *J.*, 1954, 1442.

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tubes were examined for ultraviolet absorption at 218 mμ. The contents of tubes 61—100 were combined, the aqueous phase was extracted with chloroform (3 × 30 c.c.), and the combined extracts were dried (Na_2SO_4) and evaporated. The residue on distillation afforded the *cis*-isomer of "Phosdrin" (7·3 g.), b. p. 114°/2 mm., n_D^{20} 1·4460, $\nu_{max.}$ 897 cm.$^{-1}$. The contents of tubes 18—48 similarly gave the *trans*-isomer (2·88 g.), b. p. 112°/1 mm., n_D^{20} 1·4505, $\nu_{max.}$ 913 cm.$^{-1}$.

Benzyl cis-3-(OO-*Dimethylphosphoryloxy*)*but-2-enoate*.—Benzyl α-chloroacetoacetate was prepared from benzyl acetoacetate as described by Day [15] for the ethyl ester and had b. p. 107°/0·3 mm., n_D^{22} 1·5183 (Found: C, 56·3; H, 5·0. $C_{11}H_{11}O_3Cl$ requires C, 56·2; H, 5·1%). Trimethyl phosphite (24·8 g.) was added with stirring during 10 min. to benzyl α-chloroacetoacetate (39·9 g.). After a further 20 min. the temperature was slowly raised to 105° and the unchanged trimethyl phosphite then removed at 0·1 mm. The residue was distilled at 70° (bath-temp.)/0·0005 mm., giving *benzyl cis*-3-(OO-*dimethylphosphoryloxy*)*but-2-enoate* (41 g.), n_D^{16} 1·5083 (Found: C, 51·7; H, 5·6. $C_{13}H_{17}O_6P$ requires C, 52·0; H, 5·7%). The ester (6·0 g.), dioxan (65 c.c.), acetic acid (0·1 c.c.), and 10% palladised charcoal (0·3 g.) were stirred under hydrogen; after 6 hr. a further quantity (0·3 g.) of 10% palladised charcoal was added and the mixture stirred under hydrogen for a further 16 hr., then filtered, and evaporated. The product was shown to be essentially pure *cis*-3-(*OO*-dimethylphosphoryloxy)but-2-enoic acid by its conversion, in almost quantitative yield, into methyl *cis*-3-(*OO*-dimethylphosphoryloxy)-but-2-enoate by ethereal diazomethane, by an infrared max. (CO_2R) at 2200—3200 cm.$^{-1}$, and absence of aromatic absorption (3030, 1590, and 1500 cm.$^{-1}$).

Preparation and Reduction of Allyl 3-(OO-*Dimethylphosphoryloxy*)*but-2-enoate*.—This *ester*, b. p. 122°/0·9 mm., n_D^{16} 1·4580 (Found: C, 43·8; H, 6·3. $C_9H_{15}O_6P$ requires C, 43·3; H, 6·1%), was prepared from allyl α-chloroacetoacetate as described for the benzyl ester. Attempted hydrogenolysis gave only n-*propyl* 3-(OO-*dimethylphosphoryloxy*)*but-2-enoate*, b. p. 114° (bath-temp./14 mm.), n_D^{25} 1·4435 (Found: C, 42·5; H, 7·0. $C_9H_{17}O_6P$ requires C, 42·9; H, 6·8%), $\nu_{max.}$ 1660 (C:C) and 1722 cm.$^{-1}$ (conjugated CO) [no absorption at 3080 cm.$^{-1}$ (CH_2·CH:CH_2)].

Sodium Methyl 3-(O-*Methylphosphoryloxy*)*but-2-enoate*.—(*a*) A solution of methyl *cis*-3-(*OO*-dimethylphosphoryloxy)but-2-enoate (0·22 g.) and sodium iodide (0·158 g.) in acetone (2 c.c.) was refluxed for 5 min., giving an almost immediate precipitate (0·21 g.) which was washed with acetone and converted into the *cyclo*hexylammonium salt by use of Dowex-50 resin (*cyclo*hexylammonium form), affording after crystallisation from acetone cyclo*hexylammonium methyl* cis-3-(O-*methylphosphoryloxy*)*but-2-enoate* (0·09 g.), m. p. 137—138° (Found: C, 46·0; H, 7·5. $C_{12}H_{24}O_6NP$ requires C, 46·4; H, 8·1%).

(*b*) The *trans*-form (Ib; R = R′ = R″ = Me) (0·22 g.), when similarly treated with sodium iodide (0·158 g.), gave *sodium methyl* trans-3-(O-*methylphosphoryloxy*)*but-2-enoate* (0·171 g.) (Found: C, 30·6; H, 4·3. $C_6H_{10}O_6PNa$ requires C, 31·1; H, 4·3%).

Hydrolysis of "Phosdrin" and its Derivatives.—Titrimetric experiments. In a typical experiment a weighed sample (0·572 g.) of methyl *cis*-3-(*OO*-dimethylphosphoryloxy)but-2-enoate, dissolved in water, was stirred at 30° by means of nitrogen in a covered cell containing the electrodes of a pH meter. The pH was adjusted to 11 and kept thereat by an automatic titrating machine (Raiometer Model TT 2) and the alkali (0·025N) consumption measured at intervals. When hydrolysis was complete the contents of the cell were concentrated *in vacuo* below room temperature and examined by paper chromatography (see Tables) after detection of the phosphorus-containing products by the molybdate spray.[16] The annexed assessments (p. 2972) were made.

Partial hydrolysis. The mixed "Phosdrin" esters [60% of (Ia; R = R′ = R″ = Me) and 40% of (Ib; R = R′ = R″ = Me)] (2·5 g.) were kept at 30° for 24 hr. in M-sodium carbonate (100 c.c.); the pH of the solution fell from 11 to 8·5. The yellow solution was extracted with chloroform, and the extract dried (Na_2SO_4), evaporated, and distilled, giving a product (1·93 g.), $n_D^{22.5}$ 1·4466, shown by paper chromatography and its infrared spectrum to be mainly the *trans*-form (Ib; R = R′ = R″ = Me). The aqueous residue was brought to pH 2·4 by hydrochloric acid and extracted with chloroform (3 × 25 c.c.), dried (Na_2SO_4), and evaporated. The residue (0·48 g.) showed strong infrared absorption at 2960 cm.$^{-1}$ (CO_2H) but no P–OH band was detected at 2300 cm.$^{-1}$ (Found: equiv., 226. Calc. for $C_6H_{11}O_6P$: equiv., 210). The acid on treatment with ethereal diazomethane gave methyl *cis*-3-(*OO*-dimethylphosphoryloxy)but-2-enoate as shown by the refractive index and infrared spectrum of the distilled product.

[15] Day, *J.*, 1915, 1646.
[16] Hanes and Isherwood, *Nature*, 1949, **164**, 1107.

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Ester hydrolysed	Conditions	Products	Proportion
Ia; R = R′ = R″ = Me	pH 11, 3 hr.	Ia; R = R′ = R″ = Me	5
		Ia; R = H, R′ = R″ = Me	1
		Ia; R = R′ = Me, R″ = H	1
		Me_2HPO_4	3
	pH 11, 24 hr.	Ia; R = H, R′ = R″ = Me	3
		Me_2HPO_4	6
		MeH_2PO_4	1
Ib; R = R′ = R″ = Me	pH 11, 3 hr.	Ib; R = R′ = R″ = Me	7
		Me_2HPO_4	2
		MeH_2PO_4	1
	pH 11, 24 hr.	Me_2HPO_4	8
		MeH_2PO_4	1
Ia; R = H, R′ = R″ = Me	pH 11, 24 hr.	Ia; R = H, R′ = R″ = Me	3
		Me_2HPO_4	5
		MeH_2PO_4	1
	pH 6, 72 hr.	Ia; R = H, R′ = R″ = Me	5
		Ia; R = R′ = H, R″ = Me *	1
		Me_2HPO_4	3
		MeH_2PO_4	1
Ia; R = R′ = Me, R″ = H	pH 11, 24 hr.	Ia; R = R′ = Me, R″ = H	5
		Ia, R = R″ = H, R′ = Me	2
		MeH_2PO_4	2
Ib; R = R′ = Me, R″ = H	pH 11, 24 hr.	Ib; R = R′ = Me, R″ = H	5
		MeH_2PO_4	5

* Prepared by anionic demethylation of (Ia; R = CH_2Ph, R′ = R″ = Me) and hydrogenolysis as described above.

Peracid-catalysed Hydrolysis of " Phosdrin."—The mixed " Phosdrin " derivatives (0·05 g.) were added to a solution of pertungstic acid [13] (30 c.c.; 2M-hydrogen peroxide + 10 mg. of WO_3) previously adjusted to pH 5·5 and the solution kept at 70° and pH 5·5. The uptake of alkali was rapid. There were obtained dimethyl hydrogen phosphate, as main product, and unchanged material. Omission of the tungstic oxide from the above reaction gave much slower uptake of alkali, and the product was shown to be (Ia; R = H, R′ = R″ = Me), with unchanged material.

Sodium Hypobromite Treatment of " Phosdrin."—A saturated solution of bromine water (40 c.c.) was adjusted to pH 9·5 with alkali, and the mixed " Phosdrin " isomers were then added (0·05 g.); the solution was kept at 20° and pH at 9·5 (titration with 0·025N-alkali). One mol. of alkali was consumed in 1 hr. and at this point the product was shown to be dimethyl hydrogen phosphate with a trace of methyl dihydrogen phosphate; alkali alone under these conditions effected negligible breakdown of " Phosdrin."

Paper Chromatography of Phosdrin and Derivatives.—Ascending chromatograms on Whatman No. 1 paper gave the annexed values for (*A*) propan-2-ol–ammonia (*d* 0·88) (2·5 : 1) and (*B*) butan-1-ol–acetic acid–water (5 : 2 : 3).

	R_F in solvent			R_F in solvent	
	A	*B*		*A*	*B*
Ia; R = R′ = R″ = Me	0·92	0·96	Ia; R = R′ = H, R = Me	0·25	0·44
Ia; R = R′ = Me, R″ = H	0·73	0·61	Ib; R = R′ = R″ = Me	0·86	0·93
Ia; R = H, R′ = R″ = Me	0·62	0·47	Ib; R = R′ = Me, R″ = H ...	0·67	0·61
Ia; R = CH_2Ph, R′ = R″ = Me	0·86	—	Me_2HPO_4	0·50	0·60
Ia; R = CH_2Ph, R′ = Me, R″ = H	0·73	—	MeH_2PO_4	0·08	0·48

We are indebted to Dr. N. Sheppard for assistance with the interpretation of infrared absorption spectra, and to the Shell Chemical Company for a gift of " Phosdrin."

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 20th,* 1958.]

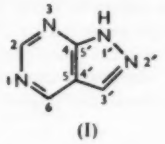
XUM

605. *Potential Purine Antagonists. Part X.* Purines and Pyrazolopyrimidines : Comparisons of Ionisation.†*

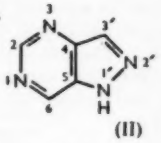
By B. M. Lynch, R. K. Robins, and (in part) C. C. Cheng.

Ionisation constants of 55 pyrazolopyrimidines have been measured, and are compared with the published values [1] for some purines. Differences in basicity, and in acidity, between similarly substituted representatives of these isomeric ring systems are discussed and interpreted. An apparent relation between anti-tumour activity (in experimental animals) and basic strength is noted for a series of amino-substituted pyrazolo(5′ : 4′-4 : 5)-pyrimidines.

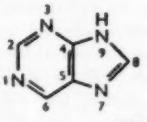
Although syntheses of several derivatives of pyrazolo(5′ : 4′-4 : 5)pyrimidine ‡ (I), pyrazolo(4′ : 5′-4 : 5)pyrimidine ‡ (II), and purine (III) have been reported recently,[1,2] and the physical properties of the purines have been investigated extensively,[1] little attention has been given to the physical properties of the pyrazolopyrimidines. Since it has been found that some 6-(substituted amino)-derivatives of (I) show promising anti-tumour activity in mice,[3] we have sought physicochemical correlations with biological activity (compare the relations between basic strength and biological activity observed with the acridines,[4] benzacridines,[5] and sulphonamides [6]), and in the present paper we have measured the basic and the acidic ionisation constants of a series of pyrazolo(5′ : 4′-4 : 5)-pyrimidines. Some substituted purines and pyrazolo(4′ : 5′-4 : 5)pyrimidines were also studied. A preliminary account of this work has already been given.†



(I)



(II)



(III)

The ionisation constants were determined by the standard ultraviolet spectrophotometric method.[7] Although the ultraviolet absorption spectra of many of the compounds studied in this paper have been recorded previously,[2,8] these measurements are of little value, since they were made with solutions of arbitrary pH values, so that the recorded spectra refer to mixtures of ions and neutral molecules, uncertain in composition. Consequently, in the present work we measured the light-absorption curves for the various species of each compound, in buffered solutions of pH values at least two units distant from the pK_a of the substance being examined.

A full account of the ultraviolet absorption spectra of the various ionic species of the substituted pyrazolo(5′ : 4′-4 : 5)pyrimidines will be given in a later paper.

* Part IX, *J. Amer. Chem. Soc.*, 1957, **79**, 6407.

† Presented in part at the Amer. Chem. Soc. Meeting, Miami, 1957, Abstracts, p. 7C.

‡ In other papers of this series,[2] Ring Index names (pyrazolo[3 : 4-*d*]pyrimidine and pyrazolo-[4 : 3-*d*]pyrimidine) were used for these ring systems. The numbering system adopted in this paper appears preferable for comparisons with the purines.

[1] (*a*) Albert and Brown, *J.*, 1954, 2060; (*b*) Brown and Mason, *J.*, 1957, 682.

[2] (*a*) Pyrazolo(5′ : 4′-4 : 5)pyrimidines: Robins, *J. Amer. Chem. Soc.*, 1956, **78**, 784; 1957, **79**, 6407; Cheng and Robins, *J. Org. Chem.*, 1956, **21**, 1240; 1958, **23**, 191. (*b*) Pyrazolo(4′ : 5′-4 : 5)pyrimidines: Robins, Furcht, Holum, Grauer, and Jones, *J. Amer. Chem. Soc.*, 1956, **78**, 2418; Robins, Holum, and Furcht, *J. Org. Chem.*, 1956, **21**, 833.

[3] Skipper, Robins, and Thomson, *Proc. Soc. Exp. Biol. N.Y.*, 1955, **89**, 594.

[4] Albert, Rubbo, Goldacre, Davey, and Stone, *Brit. J. Exp. Path.*, 1945, **76**, 160.

[5] Pages-Flon, Buu-Hoï, and Daudel, *Compt. rend.*, 1953, **236**, 2182.

[6] Bell and Roblin, *J. Amer. Chem. Soc.*, 1942, **64**, 2905.

[7] Irvin and Irvin, *ibid.*, 1947, **69**, 1091; cf. Albert and Phillips, *J.*, 1956, 1294.

[8] Falco and Hitchings, *J. Amer. Chem. Soc.*, 1956, **78**, 3143.

Experimental

Sources of Materials.—Except where otherwise stated, the compounds used were prepared as described previously,[2] and were crystallised to constant ultraviolet absorption immediately before use.

pK_a *Determinations.*—Solutions were prepared in a series of buffers, standardised by means of a Beckman Model H-2 glass electrode pH meter. The series decreased in pH down to values where the change in spectrum, corresponding to the ionisation being studied, ceased; similarly, the pH was increased in the alkaline direction. The buffer solutions were 0·01M-glycine (for pH 1·5—3·5), 0·01M-formate (for pH 2·5—3·9), 0·01M-acetate (for pH 3·8—5·7), 0·01M-phosphate (for pH 5·0—7·9 and 10·3—11·3), 0·01M-borate (for pH 8·2—10·0), together with N- (pH 0) and 0·1N-hydrochloric acid (pH 1), and 0·1N- (pH 13) and 0·01N-carbonate-free potassium hydroxide (pH 12), all of which have low ultraviolet absorption.

Measurements were made with a Beckman Model DU ultraviolet spectrophotometer with matched 1-cm. cells. Buffer solutions of the same strengths as above were used as controls.

In wavelength regions selected because of marked differences between the extinction coefficients of the protonated (ε_{MH+}) and unprotonated species (ε_M) (*i.e.*, cation and neutral molecule, or neutral molecule and anion), the extinction coefficients of the sum of the two species (ε) were measured at 1 mμ wavelength intervals; the pH values of the solutions used were chosen so as to correspond to the range from 15% to 85% protonation. The pK_a's were determined by using the following formula:

$$pK_a = pH - \log [(\varepsilon_{MH+} - \varepsilon)/(\varepsilon - \varepsilon_M)],$$

converted into antilogarithms, and averaged. This method requires no hydrolysis corrections,[7] but the usual activity corrections apply.

Results.—The ionisation constants of the various pyrazolo(5′ : 4′-4 : 5)pyrimidines and pyrazolo(4′ : 5′-4 : 5)pyrimidines, measured in water at 20°, are listed in Table 1. Compounds which are effective inhibitors of the mouse carcinoma Ad755 (as reported by Skipper and his co-workers [3,9]) are indicated by asterisks. The pK_a values of several pairs of correspondingly substituted pyrazolo(5′ : 4′-4 : 5)pyrimidines and purines are compared in Table 2. Except where otherwise stated, the values for the purines are taken from the papers of Albert and Brown [10] and of Brown and Mason.[10b]

Discussion

Previously, it has been assumed [2b] that the pyrazolopyrimidines are weaker bases than the corresponding purines, because of the large differences in basic strengths between the glyoxaline (imidazole) and pyrazole molecules (pK_a's of cations: 7·03 and 2·53 respectively; cf. Albert, Goldacre, and Phillips [10]), and programmes of synthesis [2b] seeking to prepare compounds with basicities similar to those of naturally occurring purines have been based on this assumption.

Inspection of Table 2 reveals, however, that the pyrazolo(5′ : 4′-4 : 5)pyrimidines are both slightly stronger bases (*i.e.*, their neutral molecules accept protons more readily) and slightly weaker acids (*i.e.*, their neutral molecules lose protons less readily) than the corresponding purines. From the small number of examples studied (see Table 1, part b) it appears that the pyrazolo(4′ : 5′-4 : 5)pyrimidines are stronger bases than the corresponding pyrazolo(5′ : 4′-4 : 5)pyrimidines (compare nos. 7 and 51, 48 and 52).

These results are difficult to explain if the sites of proton-acceptance in these molecules are the tertiary nitrogen atoms in the five-membered heterocyclic rings, but the elevation in pK_a on passing from the cations of purines to those of pyrazolo(5′ : 4′-4 : 5)pyrimidines can be explained satisfactorily if a nitrogen atom of the *pyrimidine ring* is the most basic centre in both systems.

If one assumes initially that the most basic centre is the 1-nitrogen atom, the electron density at this atom in a pyrazolo(5′ : 4′-4 : 5)pyrimidine would be expected to be higher than in the corresponding purine, because the electron-attracting (base-weakening) tertiary

[9] Skipper, Robins, Thomson, Cheng, Brockman, and Schabel, *Cancer Res.*, 1957, **17**, 579.
[10] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.

TABLE 1. *Ionisation constants of pyrazolo(5′ : 4′-4 : 5)pyrimidines and pyrazolo-(4′ : 5′-4 : 5)pyrimidines, in water at 20°.*

No.	Substituents		pK_a	Analytical concn. (10^{-4}M)	and wavelength range (mμ)
	(a) *Pyrazolo(5′ : 4′-4 : 5)pyrimidines.*				
1	Unsubstituted	cation	2·84 ± 0·10	1·095	250—260
		anion	9·54 ± 0·04		250—260
2	1′-Methyl	cation	2·50 ± 0·02	1·469	260—290
3	1′ : 2-Dimethyl	cation	3·27 ± 0·20	1·414	284—320
4	6-Hydroxy [a]	anion	9·38 ± 0·05	1·503	260—280
5	6-Hydroxy-1′-methyl [a]	anion	9·26 ± 0·03	1·396	276—284
6	6-Methylthio	cation	1·0 ± 0·5	0·640	240—250
		anion	9·65 ± 0·01		244—250
7 *	6-Amino	cation	4·59 ± 0·02	0·772	270—274
		anion	10·84 ± 0·05		274—290
8	2 : 6-Diamino	cation (mono)	5·58 ± 0·07	0·979	250—270
9 *	6-Methylamino	cation	4·53 ± 0·04	0·577	272—280
		anion	10·55 ± 0·10		270—280
10	2 : 6-Bismethylamino	cation (mono)	6·08 ± 0·09	1·070	250—270
11 *	6-Dimethylamino [b]	cation	4·53 ± 0·06	0·631	280—284
		anion	*ca.* 11		280—290
12 *	6-Ethylamino	cation	4·60 ± 0·05	1·265	256—266, 280—290
		anion	10·90 ± 0·04		280—288
13 *	6-Diethylamino [b]	cation	4·71 ± 0·10	0·631	276—296
14 *	6-Propylamino [c]	cation	4·58 ± 0·05	1·118	280—292
15 *	6-*iso*Propylamino	cation	4·62 ± 0·06	1·175	280—292
		anion	10·99 ± 0·10		276—284
16 *	6-Butylamino	cation	4·67 ± 0·06	1·065	274—290
		anion	11·21 ± 0·05		276—286
17 *	6-(3-Methylbutylamino) [d]	cation	4·62 ± 0·10	0·827	276—290
18 *	6-(2-Ethylhexyl)amino [d]	cation	4·60 ± 0·05	0·835	276—290
19	6-Anilino	cation	3·92 ± 0·03	1·042	290—310
20 *	6-Benzylamino	cation	4·16 ± 0·06	0·903	276—286, 296—306
		anion	10·93 ± 0·03		276—284
21 *	6-(4-Chlorobenzylamino) [d]	cation	3·96 ± 0·10	0·668	274—286, 296—310
22 *	6-Phenethylamino [d]	cation	4·38 ± 0·08	1·005	276—290
23 *	6-Furfurylamino	cation	4·01 ± 0·05	1·031	270—286, 294—312
24 *	6-Amino-1′-methyl	cation	4·32 ± 0·05	0·693	276—286
25	6-Amino-2-chloro-1′-methyl [e]	cation	2·69 ± 0·19	1·286	276—290
26	6-Amino-2-methoxy-1′-methyl	cation	3·66 ± 0·10	0·876	256—282
27 *	1′-Methyl-6-methylamino	cation	4·24 ± 0·05	1·248	280—290
28 *	6-Dimethylamino-1′-methyl	cation	4·06 ± 0·10	1·157	290—300
29 *	6-Ethylamino-1′-methyl	cation	4·24 ± 0·05	1·171	282—290
30 *	1′-Methyl-6-propylamino	cation	4·25 ± 0·07	1·072	284—300
31 *	1′-Methyl-6-*iso*propylamino	cation	4·22 ± 0·04	1·186	250—260, 286—300
32 *	6-Butylamino-1′-methyl	cation	4·22 ± 0·04	1·054	250—260, 286—300
33 *	6-Hexylamino-1′-methyl	cation	4·24 ± 0·01	0·778	280—300
34	1′-Methyl-6-(1 : 1 : 3 : 3-tetramethylbutylamino)	cation	3·96 ± 0·01	0·778	286—300
35 *	6-(2-Hydroxyethylamino)-1′-methyl	cation	3·86 ± 0·06	1·061	250—260, 286—300
36	6-Anilino-1′-methyl	cation	3·53 ± 0·05	0·920	290—310
37	6-Benzylamino-1′-methyl	cation	3·66 ± 0·15	0·865	284—298
38	6-Furfurylamino-1′-methyl	cation	3·80 ± 0·15	0·872	284—298
39	6-Amino-2-methyl	cation	5·41 ± 0·20	1·381	260—280
		anion	11·30 ± 0·10		290—300
40	2-Methyl-6-methylamino	cation	5·56 ± 0·10	1·326	270—280, 294—304
		anion	11·27 ± 0·15		270—282
41	6-Furfurylamino-2-methyl	cation	4·65 ± 0·05	0·548	290—306
42 *	6-Amino-1′-(2-hydroxyethyl)	cation	4·29 ± 0·02	1·123	270—284
43	6-Amino-1′-phenyl	cation	3·89 ± 0·02	1·150	282—290
44 *	2 : 6-Diamino-1′-phenyl	cation	4·49 ± 0·20	0·383	274—290
45	6-Amino-2-methyl-1′-phenyl	cation	4·52 ± 0·08	0·422	240—250, 276—290
46	6-Amino-1′ : 2-dimethyl	cation	5·00 ± 0·10	1·250	280—290
47	1′ : 2-Dimethyl-6-methylamino	cation	5·00 ± 0·10	1·185	280—290
48	6-Amino-3′-methyl	cation	4·61 ± 0·05	1·304	270—280
		anion	11·11 ± 0·10		296—306
49	6-Methylamino-2-methylthio	cation	3·61 ± 0·05	1·083	280—300
		anion	11·40 ± 0·10		260—280
50	6-Methoxy-1′-methyl	cation	2·51 ± 0·05	1·325	240—250

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TABLE 1. (*Continued.*)

No.	Substituents		pK_a	Analytical concn. (10^{-4}M) and wavelength range (mμ)	
	(b) *Pyrazolo*(4′ : 5′ : 4 : 5)*pyrimidines.*				
51	6-Amino	cation	5·00 ± 0·07	1·369	300—320
		anion	10·15 ± 0·10		280—300
52	6-Amino-3′-methyl	cation	5·02 ± 0·05	1·348	312—320
53	6-Benzylamino-3′-methyl	cation	4·95 ± 0·10	0·771	282—298
54	6-Furfurylamino-3′-methyl	cation	4·84 ± 0·06	0·938	284—296, 312—320
55	6-Anilino-3′-methyl	cation	4·61 ± 0·15	0·848	300—310, 332—340

[a] pK_a values of these cations were not determined, as the spectra of the cations and neutral molecules are virtually identical. [b] Decomposition by alkali made it difficult to obtain accurate values for the pK_a's of the anions of these compounds. [c] Unpublished preparation by R. K. R. [d] These compounds were prepared by Mr. C. W. Noell (unpublished work). [e] Unpublished preparation by C. C. C.

TABLE 2. *Comparisons of ionisation between purines and pyrazolo*(5′ : 4′-4 : 5)*pyrimidines.*

Purine derivative		pK_a	Pyrazolo(5′ : 4′-4 : 5)pyrimidine derivative		pK_a
Unsubstituted	cation	2·39	Unsubstituted	cation	2·84
	anion	8·93		anion	9·54
9-Methyl	cation	2·36	1′-Methyl	cation	2·50
6-Hydroxy	anion	8·94	6-Hydroxy	anion	9·54
6-Hydroxy-9-methyl	anion	9·32	6-Hydroxy-1′-methyl	anion	9·26
6-Methylthio	cation	0·0	6-Methylthio	cation	1·0
	anion	8·75		anion	9·65
6-Amino	cation	4·22	6-Amino	cation	4·59
	anion [a]	9·8		anion	10·84
2 : 6-Diamino	cation [b]	5·02 ± 0·10	2 : 6-Diamino	cation	5·58
6-Methylamino	cation	4·18	6-Methylamino	cation	4·53
	anion	9·99		anion	10·55
6-Dimethylamino	cation	3·87	6-Dimethylamino	cation	4·53
	anion	10·5		anion	*ca.* 11
2-Methyl-6-methylamino-	cation [c]	5·08 ± 0·04	2-Methyl-6-methylamino-	cation	5·56

[a] Taylor, *J.*, 1948, 765. [b] Present work: analytical concn., 1·182 × 10^{-4}M; analytical wavelength range, 288—306 mμ. Albert and Brown [12] found 5·09 (potentiometric method). [c] Present work: analytical concn., 1·081 × 10^{-4}M; analytical wavelength range, 280—290 mμ. 6-Ethylamino-2-methylpurine cation has pK_a 5·05 ± 0·10 (analytical concn., 0·663 × 10^{-4}M, analytical wavelength range 280—290 mμ). For syntheses of these compounds, see Robins, Jones, and Lin, *J. Org. Chem.*, 1956, **21**, 695.

nitrogen atom of the five-membered ring (the 2′-nitrogen atom in the pyrazolopyrimidine, and the 7-nitrogen atom of the purine) is further from, and less effectively conjugated with, the 1-nitrogen atom in the pyrazolo(5′ : 4′-4 : 5)pyrimidine than in the purine, and would therefore have less effect on the basicity of the pyrimidine-nitrogen atoms.

In the purines, the hydrogen atom is shared between the 9- and the 7-nitrogen atom, but, on an average, one of the nitrogen atoms in the glyoxaline ring is exerting a base-weakening influence on the pyrimidine-nitrogen atoms. In the pyrazolo(5′ : 4′-4 : 5)-pyrimidines, tautomeric exchange of a hydrogen atom to the 2′-nitrogen atom is unlikely, since it would involve the loss of the Kekulé resonance in the pyrimidine ring.

These explanations are essentially unaltered if the 3-nitrogen atom is the basic centre; however, for reasons to be mentioned below, we favour the 1-nitrogen atom as the predominant basic centre in both the purines and the pyrazolo(5′ : 4′-4 : 5)pyrimidines.

Some supporting evidence is available for the suggestion that a pyrimidine ring-nitrogen atom is the basic centre in the purines. The ultraviolet absorption spectra of the 7- and the 9-methylpurine cation differ markedly; [11] if cation formation involved the glyoxaline, and not the pyrimidine ring, the spectra should be almost identical. Further, it has been found that a trifluoromethyl substituent in purine is far more base-weakening

[11] Bendich, Russell, and Fox, *J. Amer. Chem. Soc.*, 1954, **76**, 6073.

from the 6- than from the 8-position, once again indicating that the pyrimidine ring is the site of proton capture.[12] Similar effects are noted with methoxy- and methylthio-purines.[1]

However, it is difficult to establish that a particular pyrimidine-nitrogen atom is the predominant basic centre in the purines and pyrazolo(5′ : 4′-4 : 5)pyrimidines; the question could be solved by *X*-ray crystallography (cf. Cochran's study [13] of adenine hydrochloride, which established that the proton is on the 1-nitrogen atom), but this technique is of course applicable only to solids, and it is possible that the position of proton-attachment in the crystal may not be identical with that in solution.

In the absence of direct experimental evidence as to the basic centres, some recent calculations [14-16] of the charge densities in these molecules using the molecular-orbital method are of interest. Mason [14] and Pullman, Pullman, and Berthier [15] have made calculations for the purine molecule, but since the results are at variance with experiment (the calculated charge densities at the various carbon atoms predict an incorrect order of reactivities towards nucleophilic reagents), little reliance can be placed on them. Mason assumed that the 7- and the 9-nitrogen atom have identical electronegativities, and this may offer a partial explanation for the discrepancy between calculation and experiment; Pullman, Pullman, and Berthier give no details of the parameters used in their calculations.

The π-electron densities calculated for the pyrazolopyrimidines [16] are listed in Table 3. The simple LCAO method, neglecting overlap, was used, with the following values for the various parameters:

$$\alpha_O = \alpha;\ \alpha_{-N=} = \alpha + \beta;\ \alpha_{-\overset{|}{N}-} = \alpha + 2\beta;\ \beta_{OO} = \beta_{ON} = \beta$$

The values chosen probably exaggerate the electronegativities of the nitrogen atoms (cf. Brown [17]), *i.e.*, the true charge migrations are smaller than they appear to be, but the relative values should be unaffected by this choice.

TABLE 3. *π-Electron densities in the pyrazolopyrimidines.*

(a) *Pyrazolo*(5′ : 4′-4 : 5)*pyrimidine.*				(b) *Pyrazolo*(4′ : 5′-4 : 5)*pyrimidine.*			
Position	π-Electron density	Position	π-Electron density	Position	π-Electron density	Position	π-Electron density
1′	1·71	1	1·34	1′	1·70	1	1·33
2′	1·35	2	0·75	2′	1·29	2	0·78
3′	0·87	3	1·36	3′	0·90	3	1·35
4′ (=5)	1·01	6	0·73	4′ (=4)	0·92	6	0·76
5′ (=4)	0·88			5′ (=5)	0·97		

The results are in good agreement with experiment, predicting that 6-substituents would be preferentially attacked by nucleophilic reagents, and can therefore be regarded with some confidence. The π-electron densities are highest at the 3-nitrogen atoms, and it would therefore be expected that these atoms would be the predominant sites of proton-attachment in the pyrazolopyrimidines, in the absence of other factors. However, the π-electron densities in the neutral molecules may not be the controlling factor in determining the preferred sites of protonation; the magnitude of resonance-stabilisation of the various possible cations (over and above that prevailing in the neutral molecules), *i.e.*, the " additional ionic resonance " effect (cf. Albert, Goldacre, and Phillips [10]) may be the most important factor. Thus, protonation at the 1-nitrogen atom in purine or pyrazolo-(5′ : 4′-4 : 5)pyrimidine introduces a base-strengthening additional ionic resonance of a *para*-quinonoid type (structures VIIa, b; VIIIa, b), while protonation at the 3-nitrogen atom would lead to the less effective *ortho*-quinonoid type of additional ionic resonance

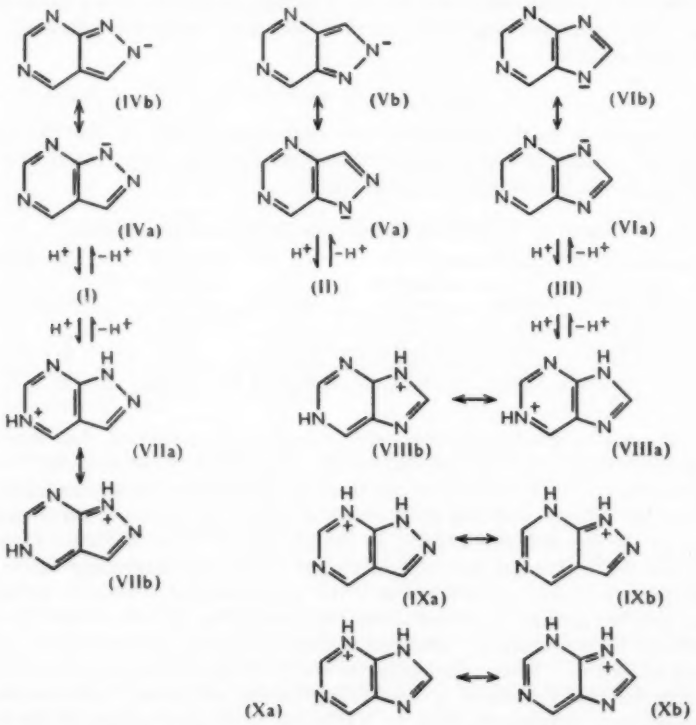
[12] Bendich, Giner-Sorolla, and Fox, Ciba Foundation Symposium, " The Chemistry and Biology of Purines," Churchill Ltd., London, 1957, p. 3.
[13] Cochran, *Acta Cryst.*, 1951, **4**, 81.
[14] Mason, ref. 12, p. 72.
[15] Pullman, Pullman, and Berthier, *Compt. rend.*, 1956, **243**, 380.
[16] Unpublished calculations by Dr. A. J. Owen (see Table 3).
[17] Brown, *J.*, 1956, 272.

XUM

(structures IXa, b; Xa, b). We suggest, therefore, that the cations of purines and pyrazolo(5′ : 4′-4 : 5)pyrimidines have structures of types VII and VIII. The structures resemble those deduced for the 4-aminopyrimidine cation, where the basic strength, ultraviolet absorption spectra, and ease of methylation at the 1-position, all suggest that protonation occurs at the 1-nitrogen atom, leading to the generally preferred *para*-quinonoid type of additional ionic resonance.[18]

It is, of course, realised that an equilibrium may exist between the various possible cations. By proposing that the 1-nitrogen atoms of purines and pyrazolo(5′ : 4′-4 : 5)-pyrimidines are the basic centres, we imply only that these nitrogen atoms are protonated in the *predominating* cations.[19] It should be pointed out, however, that a nitrogen atom participating in *para*-quinonoid additional ionic resonance will be the predominating basic centre when compared with a corresponding *ortho*-quinonoid system. Relevant examples[10] are: 2-aminopyridine (*ortho*-quinonoid), pK_a 6·86, 4-aminopyridine (*para*-quinonoid), pK_a 9·17; 2-aminoquinoline (*ortho*-quinonoid), pK_a 7·34, 4-aminoquinoline (*para*-quinonoid), pK_a 9·17.

The similar basic strengths of purine, pyrazolo(5′ : 4′-4 : 5)pyrimidine, and 1 : 2 : 3-triazolo(5′ : 4′-4 : 5)pyrimidine (XI) (pK_a of cation, 2·1)[12,20] can be attributed to the



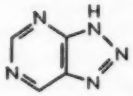
para-quinonoid additional ionic resonance common to the cations derived from all three ring systems. The importance of this effect is well illustrated by comparing the pK_a's of the cations of pyrazolo(5′ : 4′-4 : 5)pyrimidine (2·84) and indazole (XII) (approx. 1·3),[10]

[18] Brown, Hoerger, and Mason, *J.*, 1955, 4035.
[19] Cf. Osborn, Schofield, and Short, *J.*, 1956, 4191.
[20] Felton, "Recent Work on Naturally Occurring Nitrogen Heterocyclic Compounds," *Chem. Soc. Special Publ.*, No. 3, 1955, p. 134.

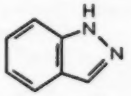
XUM

and the values for the triazolopyrimidine (XI) and benzotriazole (XIII) (1·6).[10] In these examples, replacement of two aromatic carbon atoms by normally base-weakening nitrogen atoms has given rise to increases in basicity. This result is ascribed to the additional ionic resonance in the cations of (I) and (XI), which obviously cannot contribute to basic strength in the indazole and benzotriazole cations.

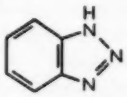
In the 6-substituted-aminopyrazolo(5′ : 4′-4 : 5)pyrimidines (XIV; R^1 and R^2 = H, alkyl, or aryl) (nos. 7, 9, 11—23), relatively large increases in the pK_a's of the cations over the value for the parent compound (I) (about 2 units of pK) indicate that some further stabilisation of the cations relative to the neutral molecules is present. The increases can be understood readily in terms of protonation at the 1-nitrogen atoms to yield amidine-type structures, once again stabilised by additional ionic resonance, as exemplified



(XI)



(XII)



(XIII)

by the canonical forms (XVa, b, c). Analogous base-strengthening by amino-substituents is observed with the purines.[1a]

The differential effects of methyl groups in the pyrimidine and the pyrazole ring of pyrazolo(5′ : 4′-4 : 5)pyrimidines lend further supporting evidence to the suggestion that the site of protonation is in the pyrimidine ring. Insertion of a methyl group into a nitrogen-heterocyclic molecule generally gives rise to an appreciable base-strengthening effect (from 0·3 to 1 unit of pK) if it is α or γ to the basic centre (*e.g.*, the quinoline [21] and acridine [22] series). 6-Amino-3′-methylpyrazolo(5′ : 4′-4 : 5)pyrimidine (no. 48) has virtually the same basic strength as the 6-amino-compound (no. 7), but 6-amino- and 6-methylamino-2-methylpyrazolo(5′ : 4′-4 : 5)pyrimidines (nos. 39 and 40), and the 6-alkylamino-2-methylpurines (Table 2) show large elevations in pK_a over the corresponding compounds lacking a methyl group in the pyrimidine ring (compare also nos. 2 and 3, 23 and 41, 43 and 45), indicating very strongly that protonation occurs in the pyrimidine ring in both the pyrazolo(5′ : 4′-4 : 5)pyrimidines and the purines.

The basicities of the various alkylamino- and arylamino-substituted pyrazolo(5′ : 4′-4 : 5)pyrimidines are more or less as expected, and where comparisons can be made, follow similar sequences to those recorded for the purines.[1a] Mono- and di-alkylation of the amino-group does not greatly affect the basic strength, while the 6-anilino-, 6-benzylamino-, and 6-phenethylamino-compounds (nos. 19, 20, and 22) reveal the decreased base-weakening effect of a phenyl group as it is further separated from the basic centre. Further substitution by amino-groups increases the base-strengthening effect (as compared with the parent compound), as a result of the obvious additional resonance-stabilisation of the cations (the new amino-group provides a further seat for the positive charge). A 2-amino-substituent has approximately the same base-strengthening effect as a 2-methyl group (compare nos. 8 and 39, 10 and 40, 44 and 45), and an analogous relationship holds for suitably substituted purines (Table 2).

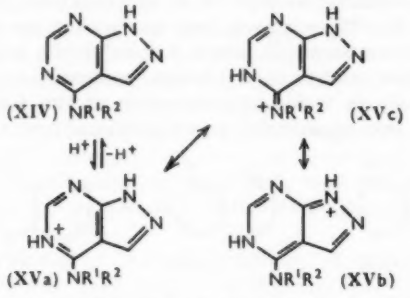
Chloro- and methylthio-groups are base-weakening, as expected from their effects in benzenoid systems (compare nos. 24 and 25, 1 and 6, 9 and 49), while a 6-methoxy-substituent seems to have little effect (nos. 2 and 50); a 2-methoxy-substituent is, surprisingly, appreciably base-weakening (nos. 24 and 26).

Substitution of the 1′-hydrogen atom in pyrazolo(5′ : 4′-4 : 5)pyrimidines by a methyl group results in a small decrease in basic strength (*ca.* 0·3—0·5 unit of pK) for many compounds (compare nos. 1 and 2, 7 and 24, 9 and 27, 11 and 28, 12 and 29, 14 and 30, 15 and 31, 16 and 32, 23 and 38, 19 and 36, 20 and 37, 39 and 46, 40 and 47). It is possible

[21] Felsing and Biggs, *J. Amer. Chem. Soc.*, 1933, **55**, 3624.
[22] Albert and Goldacre, *J.*, 1946, 706.

XUM

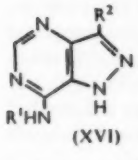
that this base-weakening is a result of the lowering of the resonance energy of the cations, because of the non-equivalence (lack of symmetry) of the 1- and 1′-nitrogen atoms in the cations derived from the methylated compounds [compare the similar (small) base-weakening effects arising from *N*-alkylation of guanidine [23]]. Steric interference with the coplanarity of the pyrimidine and pyrazole rings, leading to less effective conjugation,



could also explain these observations, and Stuart–Briegleb models show that there is interference between the 3-nitrogen atom and a 1′-methyl group in the 1′-methylpyrazolo-(5′ : 4′-4 : 5)pyrimidines. The basic strengths of two of the 6-alkylamino-1′-methylpyrazolo(5′ : 4′-4 : 5)pyrimidines [no. 34, 1′-methyl-6-(1 : 1 : 3 : 3-tetramethylbutylamino-)pyrazolo(5′ : 4′-4 : 5)pyrimidine, and no. 35, 6-(2-hydroxyethylamino)-1′-methylpyrazolo-(5′ : 4′-4 : 5)pyrimidine] are appreciably lower than would be expected by comparison with the other compounds in this series. The decreased basic strength of no. 34 can be explained by steric interference to protonation at the 1-nitrogen atom, caused by the highly branched 6-alkylamino-group, and that of no. 35 in terms of intramolecular hydrogen-bonding between the 1-nitrogen atom and the hydroxy-group of the 6-(2-hydroxyethylamino)-substituent. Base-weakening due to intramolecular hydrogen-bonding has been noted previously.[10,19,24]

Introduction of 1′-phenyl groups into the pyrazolo(5′ : 4′-4 : 5)pyrimidines leads to decreased basic strengths (compare nos. 7 and 43, 8 and 44, 39 and 45), readily explained by the electron-attracting effect of such groups.

The 6-aminopyrazolo(4′ : 5′-4 : 5)pyrimidines (XVI; R^1 = H, alkyl, or Ph, R^2 = H or Me) are stronger bases than the corresponding purines and pyrazolo(5′ : 4′-4 : 5)pyrimidines (compare the following pK_a's for the appropriate cations: no. 51, 5·00; adenine, 4·22; no. 7, 4·59; also nos. 52, 5·02, and 48, 4·61), perhaps indicating that the site of protonation in the pyrazolo(4′ : 5′-4 : 5)pyrimidines differs from that in the purines and pyrazolo(5′ : 4′-4 : 5)pyrimidines. The similarities in basic strength between nos. 51 and 52 indicate, however, that the pyrazole ring does not accept a proton. Close resemblance between the ultraviolet absorption spectra of the cations of purines [25] and pyrazolo(5′ : 4′-4 : 5)-pyrimidines,[26] and the marked difference between the spectra of these two systems and the corresponding pyrazolo(4′ : 5′-4 : 5)pyrimidines,[26] support the suggestion that the pattern of protonation in the latter compounds is different from that observed with the purines and pyrazolo(5′ : 4′-4 : 5)pyrimidines.



(XVI)

Turning now to a discussion of the pK_a values of the neutral molecules of the pyrazolopyrimidines and purines (*i.e.*, their relative acidic strengths), it is relatively easy to explain the greater acid strengths of the purines when compared with the corresponding pyrazolopyrimidines (cf. Table 2). In the purines, the negative charge of the anion may be shared

[23] Angyal and Warburton, *J.*, 1951, 2492.
[24] Short, *J.*, 1952, 4584.
[25] Mason, *J.*, 1954, 2071.
[26] Lynch, unpublished results.

between the two glyoxaline-nitrogen atoms without losing the Kekulé resonance associated with the pyrimidine ring (structures VIa, b), but in the pyrazolo-(5′ : 4′-4 : 5)- and -(4′ : 5′-4 : 5)-pyrimidines, structures where the 2′-nitrogen atoms carry the negative charge (*e.g.*, IVb, Vb) cannot maintain the aromatic character of the pyrimidine ring. The effects of substituents on acid strengths in the pyrazolo(5′ : 4′-4 : 5)pyrimidines are more or less as expected; amino-groups and methyl groups are acid-weakening; however, methylthio-substitution causes slight acid-weakening, in contrast to observations in the purine series [1a] (cf. nos. 1 and 6, 9 and 49).

Introduction of a hydroxyl group (leading to the possibility of tautomerism to an amide) into the pyrazolo(5′ : 4′-4 : 5)pyrimidine molecule (*e.g.*, no. 4) makes feasible the formation of several different anions. As Albert and Brown [1a] found with the corresponding purine, it is difficult to determine which hydrogen atom ionises preferentially, since the pK_a's of the neutral molecules of pyrazolo(5′ : 4′-4 : 5)pyrimidine, its 6-hydroxy-derivative (no. 4), and 1′-methyl-6-hydroxy-derivative (no. 5) are all closely similar.

The anti-tumour activity of several 6-(substituted amino)pyrazolo(5′ : 4′-4 : 5)-pyrimidines has been reported previously; [3,9] the " starred " compounds listed in Table 1 are all strong inhibitors of growth of the mouse Adenocarcinoma 755, *i.e.*, at dose levels which are not appreciably toxic (less than 10% mortality) they effect reduction in tumour weight to a level less than 20% of that in untreated control animals. Details of the biological testing of the various pyrazolo(5′ : 4′-4 : 5)pyrimidines and pyrazolo(4′ : 5′-4 : 5)-pyrimidines listed in Table 1 are given in the recent paper by Skipper and his co-workers.[9] Reference to Table 1 shows that anti-tumour activity (as measured by inhibition of Adeno-carcinoma 755) is virtually confined to compounds whose cations have pK_a's between 4·0 and 4·7. It seems, therefore, that one important factor in determining anti-tumour activity in these compounds is the basic strength, which must approximate to that of adenine; of course, other factors are obviously of importance, *e.g.*, methyl groups in the 2- or 3′-position result in complete loss of activity, and none of the pyrazolo(4′ : 5′-4 : 5)-pyrimidines are active, although no. 55 falls within the prescribed limits of basicity.

There is abundant evidence of competition between adenine and 6-aminopyrazolo-(5′ : 4′-4 : 5)pyrimidine in biological systems: 6-aminopyrazolo(5′ : 4′-4 : 5)pyrimidine is an antimetabolite of adenine in *Neurospora crassa* [27] and *Lactobacillus arabinosus*; [9] also, damage produced by 6-aminopyrazolo(5′ : 4′-4 : 5)pyrimidine in tissue culture experiments on the Hela strain of human cervical carcinoma is relieved by flavine-adenine dinucleotide.[28]

On the basis of this information, it seems probable that the 6-(substituted amino)-pyrazolo(5′ : 4′-4 : 5)pyrimidines owe their biological activity to interference with the utilisation of adenine or some adenine derivative, but far more experimental work is necessary before the mechanism of action of these purine analogues can be established. The present work merely indicates an association between basic strength and biological activity which may merit further investigation, and we hope to extend our studies to other purine analogues with similar basic strengths to the 6-substituted-amino-pyrazolo-5′ : 4′-4 : 5)pyrimidines.

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Chemistry Department, New Mexico Highlands University,
Las Vegas, New Mexico, U.S.A.
[Present addresses: (B. M. L.) Chemistry Department,
St. Francis Xavier University,
Antigonish, Nova Scotia, Canada.
(R. K. R.) Department of Chemistry, Arizona State College,
Tempe, Arizona, U.S.A.] [*Received, January 24th*, 1958.]

[27] Fuerst, Somers, and Hsu, *J. Bact.*, 1956, **72**, 387.
[28] Hsu, personal communication.

XUM

606. *Molecular Rearrangements. Part II.** 2 : 6-*Disubstituted* N-*Chloroacetanilides.*

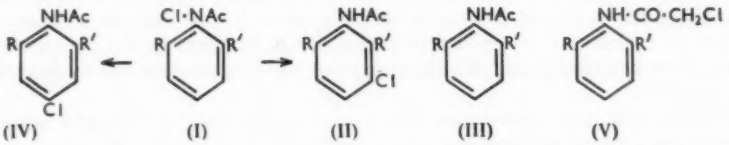
By C. Beard and W. J. Hickinbottom.

meta-Migration of chlorine occurs when *N*-chloro-2 : 6-dimethyl- or -diethyl-acetanilide is heated in acetic acid. With *N* : 2 : 6-trichloroacetanilide under similar conditions, there is no substitution in the nucleus; instead the labile chlorine attacks the solvent and the acyl group, to give chloroacetic acid and the 2 : 6-dichloroanilides of mono- and di-chloroacetic acid. These observations, which are unexpected on the basis of an intramolecular course for the proton-catalysed rearrangement of *N*-chloroacylarylamines, are simply explained by assuming that this rearrangement is an intermolecular chlorination.

In contrast to the *meta*-migration induced by proton-catalysis, the rearrangement of *N*-chloro-2 : 6-dimethyl- and -diethyl-acetanilide promoted by benzoyl peroxide occurs with some difficulty and the chlorine is transferred to the *para*-position.

The activating effect of an amino- or acetamido-group on the benzene ring is known to be diminished by substituents in the 2- and the 6-position,[1] *e.g.*, in 2 : 6-disubstituted *NN*-dialkylanilines the *para*-position is inert, or relatively so, towards nitrous acid, diazo-coupling, and condensation with aldehydes.[2,3] Of special significance to the present investigation is the relatively high proportion of electrophilic substitution *meta* to the acetamido-group in 2 : 6-dimethylacetanilide: nitration gives 2 : 6-dimethyl-3-nitro-acetanilide;[4,5,6] bromination yields a mixture of 3- and 4-bromo-compounds.[5,6,7] It is now found that 2 : 6-dimethyl- and 2 : 6-diethyl-acetanilide are chlorinated in glacial acetic acid in the *meta*-position to the amido-group.

This provides a test of the view [8] that the rearrangement of *N*-arylchloroacylamides is, not an intramolecular rearrangement, but an intermolecular chlorination. On this view the proton-catalysed change brought about by heating *N*-chloro-2 : 6-dimethylacetanilide



(I; R = R′ = Me) in acetic acid should give 3-chloro-2 : 6-dimethylacetanilide (II; R = R′ = Me), the same product as is obtained from 2 : 6-dimethylacetanilide by molecular chlorine in acetic acid. This has been verified experimentally and confirmed by the behaviour of *N*-chloro-2 : 6-diethylacetanilide (I; R = R′ = Et) and of *N* : 2-dichloro-6-methylacetanilide (I; R = Me, R′ = Cl) under similar conditions. In all these changes, the chlorine moves from the nitrogen to the position *meta* to the amido-group. The results are summarised in the Table.

The behaviour of *N* : 2 : 6-trichloroacetanilide (I; R = R′ = Cl) is of special interest in that no migration of the *N*-chlorine to the nucleus has been observed when it is heated

* Part I, *J.*, 1957, 2981.

[1] Ingham and Hampson, *J.*, 1939, 981.
[2] Friedlander, *Monatsh.*, 1898, **19**, 627.
[3] von Braun, *Ber.*, 1916, **49**, 1101; 1918, **51**, 282.
[4] Nolting and Stocklin, *Ber.*, 1891, **24**, 568.
[5] Nolting, von Braun, and Thesmar, *Ber.*, 1901, **34**, 2262.
[6] Wepster, *Rec. Trav. chim.*, 1954, **73**, 810.
[7] Dadswell and Kenner, *J.*, 1927, 1105.
[8] Ayad, Beard, Garwood, and Hickinbottom, *J.*, 1957, 2981.

with acetic acid. Instead chlorination takes place in the acetyl group to give the 2 : 6-dichloroanilides of mono- and di-chloroacetic acid; chlorination of the solvent also takes place with the formation of chloroacetic acid. The simplest interpretation is that when the reactivity of the nucleus is reduced sufficiently, the *N*-chloroamido-group can chlorinate in other directions. This is indeed what is to be expected from other observations

Reactions of N-*chloroacetanilides.*

Starting material (I)		Products	
R	R′	Formed in AcOH	Formed under free-radical conditions
Me	Me	(II)	(III) 60%; (IV) 30%; (II) 10%
Et	Et	(II)	(III) 70%; (IV) 23%; *o*-C_6H_4Et·NHAc 7%
Me	Cl	(II) & (V)	(III) 75%; (I) 3%
Cl	Cl	(III) & (V) 2 : 6-$C_6H_3Cl_2$·NH·CO·$CHCl_2$ $CH_2Cl·CO_2H$	

reported in this paper and from our general conclusions [8] on the nature of the reactions of *N*-chloroacylarylamines in general.

Some free chlorine is indeed formed when *N* : 2 : 6-trichloroacetanilide is heated in acetic acid. The quantity is small and arises probably from a side reaction. Indeed chlorination of *p*-xylene or mesitylene in acetic acid by *N* : 2 : 4 : 6-tetrachloroacetanilide could not be halted by passing a stream of nitrogen through the solution: very little chlorine or hydrogen chloride is detected when the issuing nitrogen is passed through aqueous silver nitrate.

The rearrangement of *N*-chloro-2 : 6-dimethylacetanilide promoted by benzoyl peroxide should give, on our hypothesis, 4-chloro-2 : 6-dimethylacetanilide (IV; R = R′ = Me) although the transference of the chlorine to the nucleus should be seriously hampered by the two *o*-alkyl groups which restrict conjugation of the acetamido-group with the nucleus. Indeed chlorine migrates to the *para*-position, though the yield is low and the product contains also 2 : 6-dimethylacetanilide (III; R = R′ = Me) and a small proportion of 3-chloro-2 : 6-dimethylacetanilide (II; R = R′ = Me). Under similar conditions, *N*-chloro-2 : 6-diethylacetanilide (I; R = R′ = Et) gives a relatively poor yield of the expected chloro-compound (IV; R = R′ = Et): the product is largely 2 : 6-diethylacetanilide (III; R = R′ = Et) with, unexpectedly, a small amount of 2-ethylacetanilide. A search for 2-ethylaniline in the 2 : 6-diethylaniline used in this work established its absence, nor is it formed by acid hydrolysis of 2 : 6-diethylacetanilide; it is, indeed, a product of the reaction. There are at least two alternative schemes to account for its formation, but neither is offered as explanation until more experimental evidence is available.

Experimental

Rearrangement of N-*Chloro*-2 : 6-*dimethylacetanilide.*—(a) *In acetic acid.* *N*-Chloro-2 : 6-dimethylacetanilide [9] melted at 112—113° (Found: active Cl, 17·8. Calc. for $C_{10}H_{12}ONCl$: Cl, 17·9%).

(i) A solution of it (3 g.) in acetic acid (30 c.c.) was stored at 50° in the dark. After a week, when there was no longer any positive reaction for active chlorine, the solution was diluted with water and the precipitate collected, washed, and dried. It consisted essentially of 3-chloro-2 : 6-dimethylacetanilide; the m. p. of the crude product was 138—145°, raised to 148—149·5° by three crystallisations from benzene.

The identity was established by direct comparison with a specimen prepared by acetylation of the amine (m. p. 71—72°; Dadswell and Kenner [7] give m. p. 72—73°) obtained by hydrogenation of 4-chloro-2-nitro-*m*-xylene. The authentic acetyl derivative melted at 148·5—150° (Dadswell and Kenner [7] give 146—147°).

(ii) For comparison, 2 : 6-dimethylacetanilide was chlorinated in glacial acetic by slowly evaporating into the solution, at 50°, the calculated amount of liquid chlorine. The product, after two crystallisations from benzene, had m. p. and mixed m. p. 149—150°.

[9] Dewar and Scott, *J.*, 1955, 1845.

XUM

(iii) Chlorine was passed through a suspension of 2 : 6-dimethylacetanilide (16·3 g.) in boiling carbon tetrachloride till all the solid had dissolved. The solid residue obtained on evaporation was hydrolysed by boiling aqueous sulphuric acid (60% v/v) for 24 hr., and the resulting amines (10·5 c.c.) recovered by steam-distillation after basification. Distillation through a Haage spinning-band column gave the following main fractions: (*a*) 2 : 6-dimethylaniline, b. p. 113°/28·5 mm. (acetyl derivative, m. p. and mixed m. p. 180·5—181·5°); (*b*) 3-chloro-2 : 6-dimethylaniline, b. p. 148—150°/29 mm. (acetyl derivative, m. p. and mixed m. p. 148—149°); and (*c*) 4-chloro-2 : 6-dimethylaniline, m. p. 47—47·5°, b. p. 153°/29 mm. (acetyl derivative, m. p. and mixed m. p. 195·5—197°). It is estimated that the ratio of 4- to 3-chloro-2 : 6-dimethylacetanilide in the product is approximately 3 : 1.

(b) *With benzoyl peroxide.* A solution of *N*-chloro-2 : 6-dimethylacetanilide (49·4 g.) in carbon tetrachloride (125 c.c.) containing 0·6 g. of benzoyl peroxide was refluxed in the dark until there was a negative test for active chlorine (3 days). The solid remaining after evaporation was a mixture which could not be resolved satisfactorily by crystallisation. It was hydrolysed by boiling aqueous sulphuric acid (60% v/v) for 18 hr. and the amines obtained were distilled through a Haage spinning-band column, giving: (*a*) 2 : 6-dimethylaniline, b. p. 115·5°/37·5 mm. [acetyl derivative, m. p. and mixed m. p. 180·5—181·5° (Found: C, 73·6; H, 8·3; N, 8·6. Calc. for $C_{10}H_{13}ON$: C, 73·5; H, 8·0; N, 8·6%)]; (*b*) 3-chloro-2 : 6-dimethylaniline, b. p. 144—148°/37·5 mm. (acetyl derivative, m. p. and mixed m. p. 148·5—150°); and (*c*) 4-chloro-2 : 6-dimethylaniline, b. p. 154—155°/37·5 mm. [acetyl derivative, m. p. and mixed m. p. 195·5—197·5° (Found: C, 61·0; H, 6·2; N, 7·0; Cl, 17·6. Calc. for $C_{10}H_{12}ONCl$: C, 60·7; H, 6·1; N, 7·1; Cl, 17·9%)].

The approximate composition of the amine mixture deduced from the weights of the distillation fractions is given in the Table.

For the identification of 4-chloro-2 : 6-dimethylacetanilide, a specimen was made from the amine prepared by Dadswell and Kenner's method.[7]

Rearrangement of N-*Chloro*-2 : 6-*diethylacetanilide.*—2 : 6-Diethylaniline was a commercial sample, b. p. 109°/10·5 mm., n_D^{16} 1·5466; and its acetyl derivative melted at 139—140°. Ecke *et al.*[10] give b. p. 235—236°, n_D^{20} 1·5461 (acetyl derivative, m. p. 135—136°).

N-*Chloro*-2 : 6-*diethylacetanilide* was prepared by shaking a suspension of finely powdered 2 : 6-diethylacetanilide (20 g.) with 0·45N-potassium hypochlorite (250 c.c.). After 2 hr., the suspended solid was removed in chloroform (30 c.c.) and shaken with two lots of 0·45N-hypochlorite (250 c.c.), each for 2 hr. Evaporation of the washed and dried chloroform solution left *N*-chloro-2 : 6-diethylacetanilide, m. p. 38·5—39·5° after crystallisation from light petroleum (b. p. <40°) (Found: C, 64·0; H, 7·1; N, 6·2; Cl, 15·5; active Cl, 15·6. $C_{12}H_{16}ONCl$ requires C, 63·8; H, 7·1; N, 6·2; Cl, 15·7%).

(a) *In acetic acid.* A solution of the *N*-chloro-compound (5 g.) in acetic acid (12 c.c.) was stored at 70° in the dark. There was no positive test for active chlorine after 44 hr. The product precipitated by water was essentially 3-*chloro*-2 : 6-*diethylacetanilide*, m. p. 152—153° (from, successively, aqueous alcohol, benzene, and light petroleum) (Found: C, 63·6; H, 6·9; N, 6·1; Cl, 15·9. $C_{12}H_{16}ONCl$ requires C, 63·8; H, 7·1; N, 6·2; Cl, 15·7%), identical with that obtained by chlorination of 2 : 6-diethylacetanilide in acetic acid (m. p. and mixed m. p. 152—153°). 3-*Chloro*-2 : 6-*diethylaniline* derived from it by hydrolysis with aqueous sulphuric acid (40% v/v) for 16 hr. boiled at 132—133°/11·5 mm. and had n_D^{17} 1·5617 (Found: C, 65·6; H, 7·6; N, 7·5; Cl, 19·4. $C_{10}H_{14}NCl$ requires C, 65·4; H, 7·7; N, 7·6; Cl, 19·3%).

The orientation of the halogen in the amine was established by the diazo-reaction with hypophosphorous acid and subsequent oxidation of the resulting chlorodiethylbenzene with hot aqueous permanganate. 4-Chloro*iso*phthalic acid, m. p. 296—298°, was obtained (Found: Cl, 18·2. Calc. for $C_8H_5O_4Cl$: Cl, 17·7%). Authentic 4-chloro*iso*phthalic acid was prepared by the same reactions from 2-amino-4-chloro-*m*-xylene; it had m. p. and mixed m. p. 296—298° with some previous softening (Ullmann and Uzbachian [11a] give m. p. 294°; Davies and Wood [11b] give m. p. 295°; 5-chloro*iso*phthalic acid melts at 278°).

(b) *With benzoyl peroxide.* The *N*-chloro-compound (37·6 g.), benzoyl peroxide (0·4 g.), and carbon tetrachloride (80 c.c.) were refluxed together in the dark. After 18 hr. there was a negative test for *N*-chloro-compound. Some hydrogen chloride and free chlorine were identified in the vapour above the boiling liquid. The mixed acetyl compounds left after

[10] Ecke, Napolitano, Filbery, and Kolka, *J. Org. Chem.*, 1957, **22**, 640.
[11] (*a*) Ullmann and Uzbachian, *Ber.*, 1903, **36**, 1799; (*b*) Davies and Wood, *J.*, 1928, 1126.

XUM

evaporation were hydrolysed by boiling aqueous sulphuric acid (150 c.c.; 60% v/v) for 12 hr. The amines were separated by distillation through a Haage spinning-band column into the following three homogeneous fractions: (*a*) b. p. 87—96°/10·5 mm., n_D^{16} 1·5598 (acetyl derivative, m. p. 113—113·5°, not depressed on admixture with 2-ethylacetanilide); (*b*) b. p. 109°/10·5 mm., n_D^{16} 1·5462—1·5465 (acetyl derivative, m. p. 140—140·5°, not depressed on admixture with 2 : 6-diethylacetanilide); and (*c*) b. p. 136—138°/10·5 mm., n_D^{20} 1·5728 (acetyl derivative, m. p. 175—176·5°, identical with 4-chloro-2 : 6-diethylacetanilide described below). The distillation gave also a small amount of material, b. p. 109—136°/10·5 mm. It was not possible to isolate from it any homogeneous material by crystallisation of the acetyl derivatives, so that the 3-chloro-compound was present at most as a minor constituent. The composition of the product of the rearrangement, estimated from the weights of the distillation fractions and their refractive indices, was as shown in the Table.

4-Chloro-2 : 6-diethylacetanilide was prepared by acetylating the chlorination product of 2 : 6-diethylaniline. Its m. p. (175·5—176·5°) was not depressed on admixture with the rearrangement product (Found: C, 63·5; H, 7·1; N, 6·0; Cl, 15·8. $C_{12}H_{16}ONCl$ requires C, 63·8; H, 7·1; N, 6·2; Cl, 15·7%).

Rearrangement of N : *2-Dichloro-6-methylacetanilide.*—This compound was prepared from 2-chloro-6-methylacetanilide (20 g.), m. p. 165·5—167° (Bamberger [12] gives m. p. 165—165·5°) and 0·45N-potassium hypochlorite saturated with potassium hydrogen carbonate, as described for *N*-chloro-2 : 6-diethylacetanilide. The N-*chloro-compound*, recrystallised from light petroleum (b. p. 60—80°), melts at 74—74·5° (yield, 19·6 g.) (Found: C, 49·4; H, 4·2; N, 6·6; Cl, 32·9; active Cl, 16·2. $C_9H_9ONCl_2$ requires C, 49·5; H, 4·2; N, 6·4; Cl, 32·5; active Cl, 16·25%).

(a) *In acetic acid.* The change is relatively slow in acetic acid. A solution of 5 g. in 20 c.c. of acetic acid still contained some unchanged *N*-chloro-compound after a week at 75°; during this period some free chlorine was evolved. Heating, in a sealed tube at 116°, a solution of the *N*-chloro-compound (10 g.) in acetic acid (20 c.c.) caused loss of the reaction for active chlorine in 4 days. The product precipitated by water was a mixture. Crystallisation gave no useful separation; chromatography on fuller's earth with benzene–light petroleum for elution was more satisfactory. An acetyl derivative, m. p. 150·5—151·5° after repeated crystallisation from benzene, was obtained; it represented about 30% of the original mixture and was identified as 3 : 6-*dichloro-2-methylacetanilide* by comparison with an authentic specimen (see below) (Found: C, 50·0; H, 4·0; N, 6·2; Cl, 33·0. $C_9H_9ONCl_2$ requires C, 49·5; H, 4·2; N, 6·4; Cl, 32·5%).

Chromatography on alumina with benzene–light petroleum for elution separated 3 : 6-dichloro-2-methylacetanilide and a small amount of 2-chloro-*N*-chloroacetyl-6-methylaniline (5 mg. from 3 g.), m. p. 143—144·5°.

There remained finally a considerable amount of irresolvable material, presumably a mixture of dichloro-2-methylacetanilides and 2-chloro-6-methylacetanilide. For comparison a number of the possible rearrangement products were made.

*2-Chloro-*N*-chloroacetyl-6-methylaniline.* 2-Chloro-6-methylaniline (2·8 g.) in benzene (5 c.c.) was treated with chloroacetyl chloride (1·1 g.) in benzene (5 c.c.). There was a vigorous reaction and hydrogen chloride was evolved. The mixture was kept overnight after dilution with benzene; the *product*, after crystallisation from benzene and then aqueous alcohol, melted at 143·5—144·5° alone or mixed with the rearrangement product (Found: C, 49·9; H, 4·1; N, 6·1; Cl, 32·6. $C_9H_9ONCl_2$ requires C, 49·5; H, 4·2; N, 6·4; Cl, 32·5%).

3 : 6-Dichloro-2-methylacetanilide. 3-Chloro-2-methylacetanilide (55 g.; m. p. 159—160°; lit., 157—159°) was heated with chlorosulphonic acid (120 c.c.) on a steam-bath for 90 min. and poured into ice-water. Without purification except a short washing with ice-water, the sulphonyl chloride was converted into the sulphonamide by aqueous ammonia. Hydrolysis of this (21 g.) with boiling concentrated hydrochloric acid (30 c.c.) and water (30 c.c.) for 1 hr. gave 4-amino-2-chloro-3-methylbenzenesulphonamide, m. p. 248° (from acetone and then ethyl alcohol). It (4·4 g.) was chlorinated at 60° for 25 min. with concentrated hydrochloric acid (35 c.c.), water (35 c.c.), and 30% hydrogen peroxide (2 c.c.). The crude product was boiled with 75% w/v sulphuric acid (20 c.c.) for 2 hr. to remove the sulphonic group. Steam-distillation after dilution to 100 c.c. gave 3 : 6-dichloro-2-methylaniline. Its acetyl derivative, crystallised three times from benzene, melted at 150·5—151·5° (Found: C, 49·9; H, 4·1; N, 6·1; Cl, 31·9%).

[12] Bamberger, *Annalen*, 1925, **441**, 303.

XUM

2 : 3-Dichloro-6-methylacetanilide, m. p. 161·5—162·5°, was prepared from 5-chloro-2-methylacetanilide as just described. 2 : 4-Dichloro-6-methylacetanilide, m. p. 190·5—192°, (Found: C, 49·7; H, 4·2; N, 6·5; Cl, 32·2%), was obtained by chlorination of aceto-*o*-toluidide in acetic acid at 100°. In this and similar chlorinations it was convenient to allow the necessary amount of liquid chlorine to distil slowly into the solution.

(b) *With benzoyl peroxide.* *N* : 2-Dichloro-6-methylacetanilide (10·9 g.) was heated in carbon tetrachloride (25 c.c.) containing benzoyl peroxide (0·24 g.). After 14 days' refluxing in the absence of light, with a further addition of benzoyl peroxide (0·24 g.), no *N*-chloro-compound remained. The solid obtained by evaporation was chromatographed on alumina with benzene as eluant, to give 2-chloro-6-methylacetanilide (75%) and about 3% of chloro-acetyl derivative, m. p. 143—144°, of 2-chloro-6-methylaniline. The remainder (22%) could not be resolved.

Rearrangement of N : 2 : 6-*Trichloroacetanilide.*—N : 2 : 6-*Trichloroacetanilide*, m. p. 80·5—81·5° (Found: C, 40·9; H, 2·8; N, 5·7; Cl, 44·8; active Cl, 14·8. $C_8H_6ONCl_3$ requires C, 40·3; H, 2·5; N, 5·9; Cl, 44·6; active Cl, 14·9%), was prepared by shaking finely powdered 2 : 6-dichloroacetanilide (10 g.) with 150 c.c. of bleaching powder solution (from 30 g. of bleaching powder, 500 c.c. of water, and 20 c.c. of acetic acid). After 20 min. 15 c.c. of chloroform were added, and the chloroform layer was separated after extraction of the organic matter was complete, then shaken with a further 150 c.c. of bleaching powder solution for 20 min. The operation was repeated once more. The chloroform solution was then freed from acid by repeated washing with sodium hydrogen carbonate solution, dried, and evaporated. The residue, crystallised from light petroleum (b. p. 60—80°), gave the pure *N*-chloro-compound in good yield.

(*a*) *In acetic acid.* The *N*-chloro-compound (9 g.) in acetic acid (27 c.c.) was heated in a sealed tube suspended in the vapour of boiling acetic acid. After 72 hr., the solution was deep bluish-purple; there was no gas pressure and all the *N*-chloro-compound had changed. The product precipitated by water was not amenable to separation by crystallisation. Partial resolution was achieved by chromatography on fuller's earth with benzene and benzene–ether as eluants. Three homogeneous fractions were obtained in the following order of elution: (*a*) 2 : 6-*Dichloro*-N-*dichloroacetylaniline* (0·1 g.), m. p. and mixed m. p. 171·5—173° (Found: C, 35·5; H, 1·8; N, 5·0; Cl, 51·5. $C_8H_5ONCl_4$ requires C, 35·2; H, 1·9; N, 5·1; Cl, 51·9%). (*b*) 2 : 6-*Dichloro*-N-*chloroacetylaniline*, m. p. and mixed m. p. 179—181° (0·1 g.) (Found: Cl, 44·0. C_8H_6ONCl requires Cl, 44·7%): (*c*) Impure fraction, m. p. 188—202° (~5 mg.); (*d*) 2 : 6-Dichloroacetanilide, m. p. and mixed m. p. 182—183° (0·8 g.).

For identification the 2 : 6-dichloroanilide of dichloroacetic acid was made by reaction of dichloroacetyl chloride with 2 : 6-dichloroaniline in benzene; it had m. p. 171—172° (Found: C, 35·4; H, 2·2; N, 4·9; Cl, 51·9%); the 2 : 6-*dichloroanilide* of chloroacetic acid, prepared similarly, had m. p. 178—180° (Found: C, 40·5; H, 2·1; N, 6·1; Cl, 44·7 $C_8H_6ONCl_3$ requires C, 40·3; H, 2·5; N, 5·9; Cl, 44·6%). Fraction (*a*), mixed with 2 : 3 : 4 : 6-tetrachloroaniline,[13] m. p. 181—182° (lit., between 173° and 181°), melted at 137—165°. Fraction (*b*), mixed with 2 : 3 : 6-trichloroacetanilide, m. p. 175° (Huffer [14] gives m. p. 171—173°), melted at 143—153°.

2 : 3 : 6-Trichloroaniline was obtained by hydrolysis of 1-amino-2 : 3 : 6-trichlorobenzene-4-sulphonamide, in turn obtained by chlorination of 1-amino-3-chlorobenzene-4-sulphonamide.

When it was established that chlorination could occur in the acetyl group, a search was made for chloroacetic acid in the solvent. The reaction mixture from the rearrangement of *N* : 2 : 6-trichloroacetanilide in acetic acid was diluted with light petroleum (b. p. 40—60°) to precipitate the bulk of the anilides, and the filtrate was concentrated by removal of the solvent and the bulk of the acetic acid. A brown liquid remained; it was diluted with water to precipitate all the anilide. The aqueous filtrate gave an abundant test for chloride ion after being boiled with alkali; the presence of chloroacetic acid was demonstrated by the formation of phenoxyacetic acid, m. p. and mixed m. p. 99—101°, by basifying and warming the solution with phenol.

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QUEEN MARY COLLEGE, UNIVERSITY OF LONDON, E.1. [*Received, January 28th*, 1958.]

[13] Willgerodt and Wilcke, *Ber.*, 1910, **43**, 275.
[14] Huffer, *Rec. Trav. chim.*, 1921, **40**, 457.

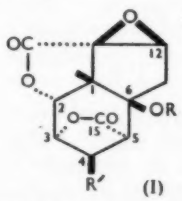
607. *Picrotoxin. Part VII.* The Chemistry of Anhydropicrotin.*

By J. S. E. Holker, Alexander Robertson, and J. H. Taylor, with (in part) K. U. Holker and W. R. N. Williamson.

An investigation on the formation and properties of anhydropicrotin and the derived anhydropicrotic acid has led us to propose structures (IV; R = H) and (VI; R = R′ = R″ = H) respectively for these compounds. The identity of anhydropicrotic and β-picrotoxinic acid has been established. Anhydropicrotin has been converted into *neo*picrotoxinin acetate and benzoate, and a re-investigation of the ozonolysis of this acetate has shown it to contain an *iso*propylidene group. Evidence is presented in favour of structures (X; R = :CMe$_2$, R′ = H) and (XII) for *neo*picrotoxinin and β-dihydropicrotoxinin respectively.

Mechanisms are suggested for the ready conversion of *neo*picrotoxinin into the aromatic compound picrotonol (XVIII), and for the formation of picrotoxinin and *neo*picrotoxinin acetates, and of anhydropicrotin by treatment of picrotin with acetic anhydride containing sulphuric acid.

The molecular compound picrotoxin, $C_{30}H_{34}O_{13}$, is readily separable into its components picrotoxinin, $C_{15}H_{16}O_6$, and picrotin, $C_{15}H_{18}O_7$.[1] Despite the recent structural elucidation of picrotoxinin (I; R = H, R′ = ·CMe:CH$_2$),[2,3] α-picrotoxinic acid (II; R = H),[2] their related bromo-derivatives,[4] and picrotoxic acid (III),[3,5] there are still many transformation products of picrotoxinin and picrotin for which the structural evidence is vague. In continuation of our studies of these products we have now investigated the reactions of anhydropicrotin and *neo*picrotoxinin and the formation of these compounds and their derivatives from picrotoxinin and picrotin.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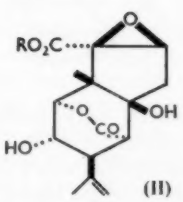
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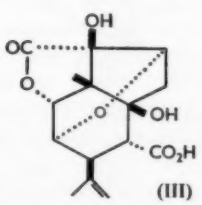

(III)

In an attempt to convert picrotin, $C_{15}H_{18}O_7$, into picrotoxinin (I; R = H, R′ = ·CMe:CH$_2$) Horrmann [6] dehydrated the former compound with phosphorus pentachloride in chloroform and obtained an isomeride of picrotoxinin which he named anhydropicrotin. We have now shown that picrotoxinin can also be converted into anhydropicrotin with hydrogen chloride in acetic acid at room temperature or with boiling 95% formic acid.

Anhydropicrotin does not react with ozone, bromine, or hydrogen in the presence of catalysts, and the infrared spectrum of this compound, although similar to that of picrotoxinin in the carbonyl stretching region, shows a total absence of double bond and hydroxyl absorptions. It therefore seems likely that in the conversion of picrotoxinin into anhydropicrotin the tertiary hydroxyl group and the *iso*propenyl double bond of the former compound have been transformed. This hypothesis is supported by the fact that picrotoxinin derivatives which lack either of these functional groups do not undergo

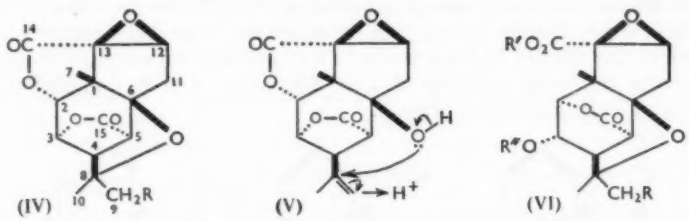
* Part VI, *J.*, 1957, 4945.

[1] Horrmann and Prillwitz, *Arch. Pharm.*, 1920, **258**, 200.
[2] Conroy, *J. Amer. Chem. Soc.*, 1951, **73**, 1889; 1952, **74**, 491.
[3] *Idem, ibid.*, 1957, **79**, 5551.
[4] *Idem, ibid.*, p. 1726.
[5] Burkhill, Holker, Robertson, and Taylor, *J.*, 1957, 4945.
[6] Horrmann, *Ber.*, 1910, **43**, 1903.

XUM

parallel reactions; thus, α-dihydropicrotoxinin (I; R = H, R′ = ·CHMe$_2$) and picrotoxinin acetate (I; R = Ac, R′ = ·CMe:CH$_2$) were recovered unchanged after attempted isomerisation. Conroy [4] has shown that bonding between the *iso*propenyl and the tertiary hydroxyl group of picrotoxinin does occur when the compound is brominated, to give bromopicrotoxinin (IV; R = Br). It therefore seemed likely that anhydropicrotin has a similar structure (IV; R = H) and is formed from picrotoxinin by the concerted mechanism shown in (V).

Horrmann [6] demonstrated that with dilute aqueous sodium hydroxide anhydropicrotin gave the monocarboxylic anhydropicrotic acid, $C_{15}H_{18}O_7$, characterised as its methyl ester. We have repeated this preparation and find that anhydropicrotic acid is identical with β-picrotoxinic acid isolated by Horrmann [7] by isomerisation of α-picrotoxinic acid (II; R = H) with 2N-sulphuric acid. Comparison of the methyl esters derived from the two acid samples confirms the identity. Thus, on the basis of structures (IV; R = H) for anhydropicrotin and (II; R = H) for α-picrotoxinic acid, β-picrotoxinic acid has structure (VI; R = R′ = R″ = H) and its ester, which can be conveniently prepared directly from anhydropicrotin by methanolysis, has structure (VI; R = R″ = H, R′ = Me). In agreement with this, methyl β-picrotoxinate showed bands at 3490 (OH), 1736 (δ-lactone), and 1720 cm.$^{-1}$ (CO_2Me) in its infrared spectrum and readily gave a monoacetate (VI; R = H, R′ = Me, R″ = Ac) which showed no hydroxyl absorption. It should be noted that the isomerisation of α-picrotoxinic to β-picrotoxinic acid would be expected to be mechanistically similar to that of picrotoxinin to anhydropicrotin.

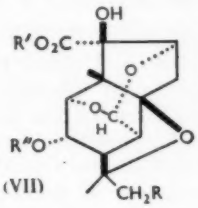


Reduction of methyl β-picrotoxinate with sodium borohydride gave a dihydro-derivative, methyl dihydro-β-picrotoxinate, showing infrared bands at 3520, 3490 (OH), and 1718 cm.$^{-1}$ (CO_2Me), but no absorption which could be attributed to a δ-lactone system. This compound formed a monoacetate having hydroxyl absorption at 3455 cm.$^{-1}$ and it is therefore apparent that methyl dihydro-β-picrotoxinate contains at least two hydroxyl groups, of which one can be readily acetylated. Treatment of methyl dihydro-β-picrotoxinate with 2N-sodium hydroxide generated dihydro-β-picrotoxinic acid which was reconverted into its ester on treatment with diazomethane. Dihydro-β-picrotoxinic acid was shown to be an α-hydroxy-acid by oxidation with lead dioxide in acetic acid to give carbon dioxide and a non-acidic ketone, $C_{14}H_{18}O_5$, characterised as its 2 : 4-dinitrophenylhydrazone. The infrared spectrum of this ketone showed bands at 3427 (OH) and 1767 cm.$^{-1}$ (attributed to a keto-group in a five-membered ring). Conroy [4] has shown that reduction of β-bromopicrotoxinic acid (VI; R = Br, R′ = R″ = H) with sodium borohydride gave a dihydro-derivative which was shown to be an α-hydroxy-acid by oxidation with lead dioxide in acetic acid to a non-acidic ketone, $C_{14}H_{19}O_5Br$, and carbon dioxide. These reactions have been interpreted by Conroy on the basis of structure (VII; R = Br, R′ = R″ = H) for β-bromo-dihydropicrotoxinic acid, which is considered to be formed from β-bromopicrotoxinic acid by attack of the borohydride anion on the carbon atom of the lactonic 14-carbonyl group, with simultaneous rearward displacement of the epoxide ring by the accumulating negative charge on the carbonyl oxygen atom. The striking similarities between the formation and properties of dihydro-β-picrotoxinic and

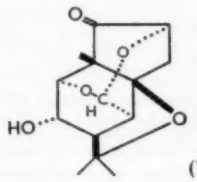
[7] Horrmann, *Ber.*, 1913, **46**, 2793.

dihydro-β-bromopicrotoxinic acid indicate that these reduction products have similar structures; consequently methyl dihydro-β-picrotoxinate, its acetate, dihydro-β-picrotoxinic acid, and the ketone derived by lead dioxide oxidation are formulated as (VII; R = R″ = H, R′ = Me), (VII; R = H, R′ = Me, R″ = Ac), (VII; R = R′ = R″ = H), and (VIII) respectively. This work also provides further support for structure (VI; R = R″ = H, R′ = Me) for methyl β-picrotoxinate.

It was reported by Horrmann [6] that treatment of anhydropicrotin with boiling benzoyl chloride gave a monobenzoate, $C_{22}H_{20}O_7$, whereas with boiling acetic anhydride and acetyl chloride a mixture of a monoacetate and a diacetate was formed. We have repeated the preparation of the monobenzoate by Horrmann's method but have been unable to effect the acetylation by his method, unchanged material being recovered in



(VII)



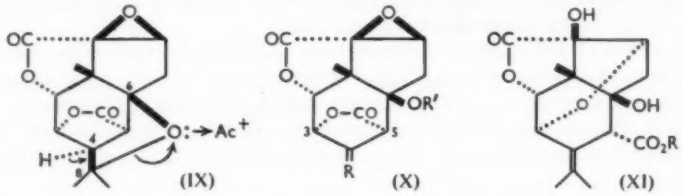
(VIII)

high yield. Treatment of anhydropicrotin with acetic anhydride and ferric chloride, however, gave a monoacetate, $C_{17}H_{18}O_7$, which had the same melting point as that reported by Horrmann for his diacetate. We have been unable to prepare a diacetate. Further investigation of our acetate showed it to be identical with *neo*picrotoxinin acetate which was first isolated by O'Donnell, Robertson, and Harland [8] from the mixture produced on treatment of a solution of picrotoxinin in acetic acid with hydrogen in the presence of a palladium catalyst and subsequent acetylation. *neo*Picrotoxinin and its acetate were further investigated by Slater *et al.*[9,10] who suggested that these compounds contain an *iso*propylidene group. This has now been confirmed by ozonolysis of *neo*picrotoxinin acetate in ethyl acetate solution to give a crystalline ozonide, m. p. 182—184° (decomp.), $C_{17}H_{18}O_{10}$, which was not decomposed by treatment with water and readily recrystallised from alcohol without decomposition. Treatment of the ozonide in ethyl acetate with hydrogen in the presence of a platinum catalyst brought about scission into acetone and a compound which analysed satisfactorily for the expected formula, $C_{14}H_{12}O_8$, after thorough drying. There seems to be little doubt that the ozonolysis product, m. p. 182—184° (decomp.), isolated by Slater [9] from *neo*picrotoxinin acetate and regarded by him as being a scission product, $C_{12}H_{12}O_7$, was the above stable ozonide, the analytical figures reported being compatible with this formulation.

The presence of an *iso*propylidene group in *neo*picrotoxinin acetate implies that its formation from anhydropicrotin (IV; R = H) involves electrophilic attack of the acetylium ion on the oxygen atom bridging positions 6 and 8, with subsequent loss of a proton from position 4, as in (IX), a reaction which is analogous to the opening of tetrahydrofurans with acetic anhydride in the presence of zinc chloride.[11] It thus appears that *neo*picrotoxinin acetate has structure (X; R = :CMe_2, R′ = Ac) and in its formation from anhydropicrotin the five-membered ether ring is opened in preference to the epoxide ring. This is in agreement with the observed remarkable stability of the epoxide ring in all picrotoxinin derivatives and has been attributed by Conroy [3] to the proximity of the 15-lactone bridge to the rear of the oxide ring, affording protection against rearward attack.

[8] O'Donnell, Robertson, and Harland, *J.*, 1939, 1261.
[9] Slater, *J.*, 1949, 806.
[10] Johns, Slater, Woods, Brasch, and Gee, *J.*, 1956, 4715.
[11] Elderfield, "Heterocyclic Compounds," Chapman and Hall, Ltd., London, 1950, Vol. I, p. 176.

On the basis of structure (X; R = :CMe_2, R′ = Ac) for *neo*picrotoxinin acetate, the derived ozonolysis product would be expected to have structure (X; R = O, R′ = Ac). However, this compound did not give a 2 : 4-dinitrophenylhydrazone and attempts to form an oxime produced an intractable water-soluble product which appeared to be a



hydroxamic acid since it gave a ruby-red ferric reaction. The infrared spectrum of the ozonolysis product, $C_{14}H_{12}O_8$, showed a band at 1701 cm.$^{-1}$, absent from the spectrum of *neo*picrotoxinin acetate and attributed therefore to an introduced ketonic carbonyl function. However, this frequency seems low for a ketone of type (X; R = O, R′ = Ac) in which the ketonic carbonyl group is present in a five-membered lactone ring. We hope to investigate further these unexpected properties and also the remarkable stability of the ozonide, but in the meantime, the evidence in favour of structure (X; R = :CMe_2, R′ = Ac) for *neo*picrotoxinin acetate, and hence, structure (X; R = :CMe_2, R′ = H) for *neo*picrotoxinin seems conclusive.

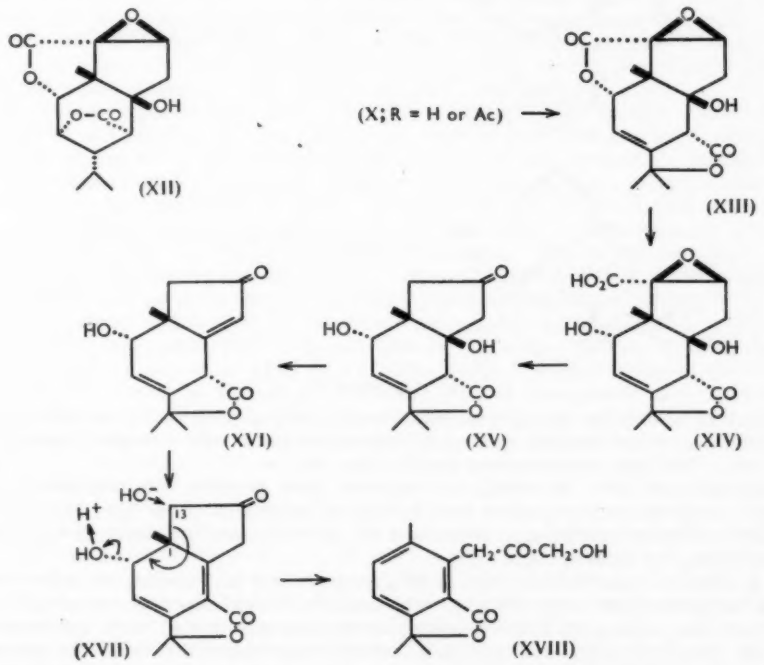
By analogy with *neo*picrotoxinin acetate, the benzoate derived from anhydropicrotin would be expected to have structure (X; R = Bz). This was supported by hydrolysis of both the acetate and the benzoate with dilute sodium hydroxide to the same crystalline acid, $C_{15}H_{18}O_7$, which gave a monomethyl ester, $C_{16}H_{20}O_7$, on treatment with diazomethane. This ester was in many respects similar to its isomer methyl picrotoxate: [5] it formed a monoacetate, decolorised bromine water without forming an insoluble monobromo-product, and was soluble in dilute sodium hydroxide solution, being reprecipitated on acidification. Its infrared spectrum showed bands at 1789 (γ-lactone) and 1738 cm.$^{-1}$ (CO_2Me). By analogy with methyl picrotoxate, the ester is named methyl *neo*picrotoxate and is tentatively formulated as (XI; R = Me). From conformational principles this type of formulation would be expected on the grounds that in both *neo*picrotoxinin acetate and picrotoxinin the oxygen atom at $C_{(2)}$ is similarly situated with respect to the epoxide ring, and therefore in the formation of both *neo*picrotoxic and picrotoxic acid the 3-hydroxyl group generated on opening of the lactone ring bridging positions 3 and 5 is in a suitable position for rearward attack at $C_{(12)}$ of the epoxide ring by an internal S_N2 mechanism.[5]

O'Donnell *et al.*[8] and subsequently Slater *et al.*[9,10] have shown that hydrogenation of picrotoxinin in the presence of a palladium–charcoal catalyst gives a mixture of two dihydro-derivatives, α- and β-dihydropicrotoxinin, together with the picrotoxinin isomer *neo*picrotoxinin (X; R = :CMe_2, R′ = H). Hydrogenation of picrotoxinin in the presence of a platinum catalyst gives α-dihydropicrotoxinin as the sole product. It seems clear that in the palladium-catalysed hydrogenation of picrotoxinin there are two competing reactions: (*a*) saturation of the *iso*propenyl system to give α-dihydropicrotoxinin (I; R = H, R′ = ·$CHMe_2$) and (*b*) isomerisation of the *iso*propenyl group to an *iso*propylidene group, leading to *neo*picrotoxinin; the latter reaction has analogies in the steroid field, *e.g.*, the isomerisation of cholest-7-enol to cholest-8(14)-enol in the presence of hydrogen and a palladium catalyst.[12] It has been shown [9] that β-dihydropicrotoxinin formed in the above palladium-catalysed hydrogenation is derived by slow saturation of the double bond in *neo*picrotoxinin. In the latter reaction it would be expected that addition of hydrogen to the double bond would occur from the least hindered side of the

[12] Wieland and Benend, *Annalen*, 1943, **554**, 1.

*neo*picrotoxinin molecule, *i.e.*, the face remote from the lactone ring bridging $C_{(3)}$ and $C_{(5)}$, thus leading to structure (XII) for β-dihydropicrotoxinin. Accordingly, this compound differs from the α-isomer only in the configuration of the *iso*propyl group at position 4. Models show that in picrotoxinin (I; R = H, R′ = ·CMe:CH_2) and α-dihydropicrotoxinin (I; R = H, R′ = ·$CHMe_2$) the tertiary hydroxyl group is sterically hindered by the *iso*propenyl and the *iso*propyl group respectively, whereas in *neo*picrotoxinin (X; R = :CMe_2, R′ = H) and β-dihydropicrotoxinin (XII) this hindrance is absent. It is thus clear why *neo*picrotoxinin and β-dihydropicrotoxinin can be readily acetylated [9] whereas picrotoxinin and α-dihydropicrotoxinin are acetylated only under forcing conditions.

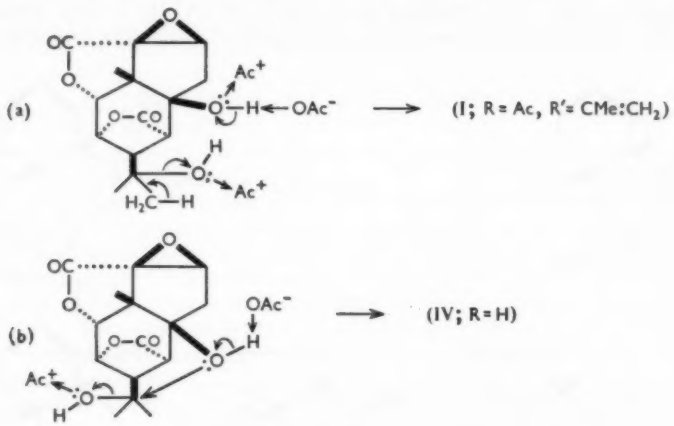
An interesting difference between the properties of picrotoxinin and its *neo*-isomer is the behaviour of these compounds with 2N-sulphuric acid. The former compound gives picrotoxic acid (III), a reaction we have already discussed,[5] whereas the latter or its acetate gives the aromatic compound picrotonol (XVIII) in high yield.[8] In this aromatisation it is considered that the driving force is probably allylic rearrangement of the 15-lactone in *neo*picrotoxinin (X; R = :CMe_2, R′ = H) to the intermediate (XIII) which is then converted into the diene (XVI) by way of the glycidic acid (XIV) and the β-hydroxy-ketone (XV). The resulting diene (XVI) or (XVII) is then aromatised by fission of the 1 : 13-bond in a carbonium-ion rearrangement, leading to picrotonol (XVIII).



Johns *et al.*[10] reported that picrotin reacts with acetic anhydride containing a trace of sulphuric acid to give *neo*picrotoxinin acetate, an unidentified monoacetate, $C_{17}H_{18}O_7$, and an insoluble compound, $C_{15}H_{16}O_6$. We find that the course of this heterogeneous reaction appears to be determined by the state of subdivision of the picrotin used. Thus, reaction of recrystallised picrotin with acetic anhydride and sulphuric acid gave a mixture from which anhydropicrotin (IV; R = H) and *neo*picrotoxinin acetate (X; R = :CMe_2, R′ = Ac) were isolated, whereas finely divided picrotin (precipitated from sodium

hydroxide with hydrochloric acid) gave a mixture from which anhydropicrotin and picrotoxinin acetate (I; R = Ac, R′ = ·CMe:CH_2) were isolated. It seems likely that the unidentified monoacetate and the " insoluble compound " of Johns *et al.* are identical with picrotoxinin acetate and anhydropicrotin respectively. Treatment of picrotin with boiling benzoyl chloride gave a mixture of *neo*picrotoxinin benzoate and anhydropicrotin.

The formation of both picrotoxinin and *neo*picrotoxinin derivatives directly from picrotin provides conclusive confirmatory evidence that the latter compound has structure (I; R = H, R′ = ·CMe_2·OH) in which the stereochemistry is identical with that of picrotoxin. It appears that picrotoxinin acetate and anhydropicrotin are formed from picrotin by competing dehydration mechanisms depicted in the annexed schemes (a) and (b) respectively, although it is not clear whether *neo*picrotoxinin acetate arises from anhydropicrotin produced in the reaction or by direct dehydration of picrotin with elimination of hydrogen from $C_{(4)}$. It should be noted that the formation of picrotoxinin acetate from picrotin appears to be the first recorded instance in which the latter compound has been converted directly into a picrotoxinin derivative containing an *iso*propenyl group.



Experimental

Ultraviolet absorption spectra were measured for 95% alcoholic solutions with a Unicam spectrophotometer and infrared spectra for mineral oil mulls with a Perkin-Elmer model 21 instrument. The light petroleum used had b. p. 60—80°.

Anhydropicrotin (IV; R = H).—(*a*) Prepared from picrotin with phosphorus pentachloride,[6] anhydropicrotin separated from acetic acid in rhombs, m. p. 322—324° (decomp.), $[\alpha]_D^{21}$ −99° (*c* 0·09 in AcOH), $\nu_{max.}$ 1783 and 1767 (shoulder) cm.$^{-1}$ (Found: C, 61·8; H, 5·4. Calc. for $C_{15}H_{16}O_6$: C, 61·6; H, 5·5%).

(*b*) A solution of picrotoxinin (1 g.) in 98% formic acid (9 ml.) was heated under reflux for 45 min. and poured into water (25 ml.). The precipitated solid was collected after 1 hr. and crystallised from acetic acid, to give anhydropicrotin in rhombs (0·4 g.), m. p. and mixed m. p. 323—325° (decomp.), $[\alpha]_D^{24}$ −100° (*c* 0·13 in AcOH). After removal of the above precipitate, the diluted reaction mixture was neutralised with sodium hydrogen carbonate and continuously extracted with ether, giving unchanged picrotoxinin, needles (0·4 g.), m. p. and mixed m. p. 204—206° (from water).

(*c*) Picrotoxinin (1 g.) in acetic acid (10 ml.) was saturated with hydrogen chloride at room temperature, then set aside overnight, and the crystals which separated were collected and recrystallised from acetic acid, to give anhydropicrotin in rhombs (0·7 g.), m. p. and mixed m. p. 324—326° (decomp.), $[\alpha]_D^{26}$ −101·5° (*c* 0·19 in AcOH). Evaporation of the acetic acid–hydrogen chloride filtrate gave unchanged picrotoxinin, needles (0·15 g.), m. p. and mixed m. p. 204—206° (from water).

Attempted isomerization of α-dihydropicrotoxinin and picrotoxinin acetate by hydrogen chloride in acetic acid as above gave unchanged starting materials in theoretical yield.

β-*Picrotoxinic Acid* (VI; R = R′ = R″ = H).—(*a*) Prepared from α-picrotoxinic acid with 2N-sulphuric acid,[7] β-picrotoxinic acid separated from water in needles, m. p. 233—234° (decomp.), $\nu_{max.}$ 1740 (δ-lactone) and 1718 cm.$^{-1}$ (CO_2H) (Found: C, 58·0; H, 6·1. Calc. for $C_{15}H_{18}O_7$: C, 58·1; H, 5·8%). Prepared with diazomethane the methyl ester separated from methanol in hexagonal plates, m. p. 226—227°, $[\alpha]_D^{19}$ −55° (*c* 1·17 in EtOH), $\nu_{max.}$ 3490 (OH), 1736 (δ-lactone), 1720 cm.$^{-1}$ (CO_2Me). Hydrolysis of the ester with aqueous 2N-sodium hydroxide regenerated β-picrotoxinic acid (m. p. and mixed m. p. 232—233°) in quantitative yield.

(*b*) Prepared from anhydropicrotin with 2N-sodium hydroxide according to Horrmann's procedure, β-picrotoxinic acid (anhydropicrotic acid) separated from acetone–benzene in needles, m. p. and mixed m. p. 231° (decomp.) [Horrmann [6] gives m. p. 221° (decomp.)]. The methyl ester formed plates, m. p. and mixed m. p. 228—230°, $[\alpha]_D^{18}$ −57° (*c* 0·89 in EtOH). The infrared spectra of this acid and its ester were identical with those of the corresponding acid and ester derived by method (*a*) above.

(*c*) To a suspension of finely powdered anhydropicrotin (1 g.) in methanol (50 ml.) was added a solution (0·7 ml.) of sodium methoxide in methanol (from 1 g. of sodium and 25 ml. of methanol), and the mixture was set aside until a homogeneous solution was formed (24 hr.). After acidification with acetic acid, the solution was evaporated, and the residue washed with water (80 ml.) and then crystallised from methanol, to give hexagonal plates (0·85 g.), m. p. 228—230°, identified as methyl β-picrotoxinate by mixed m. p. and infrared spectrum.

With acetic anhydride and pyridine methyl β-picrotoxinate gave a *monoacetate*, needles, m. p. 138—139° (from methanol) [Found: C, 59·0; H, 6·0; Ac, 11·3; OMe, 8·5. $C_{15}H_{16}O_5(OAc)(OMe)$ requires C, 59·0; H, 6·0; Ac, 11·7; OMe, 8·5%].

Methyl Dihydro-β-picrotoxinate (VII; R = R″ = H, R′ = Me).—Methyl β-picrotoxinate (4 g.) in methanol (100 ml.) and water (50 ml.) was treated with potassium borohydride (2 g.) in water (15 ml.) at 45°. After 24 hr. at room temperature the mixture was acidified with 2N-hydrochloric acid, then concentrated (60 ml.), and the crude product (5—6 g.) isolated by continuous extraction with ether (4 days). To remove boron compounds, the product was dissolved in methanol (50 ml.) containing hydrogen chloride (2 g.), heated under reflux for 45 min., and neutralised with 2N-sodium hydrogen carbonate. *Methyl dihydro-β-picrotoxinate* was isolated by continuous extraction with ether (24 hr.), dried by azeotropic distillation with benzene, and crystallised from ethyl acetate–light petroleum, forming needles (1·9 g.), m. p. 233—234° (depressed to 191—194° on admixture with methyl β-picrotoxinate), $[\alpha]_D^{20}$ −67·8° (*c* 0·98 in EtOH), $\nu_{max.}$ 3520, 3490 (OH) and 1718 cm.$^{-1}$ (CO_2Me) (Found: C, 59·0; H, 7·0; OMe, 10·1. $C_{16}H_{22}O_7$ requires C, 58·9; H, 6·8; OMe, 9·5%). Methyl dihydro-β-picrotoxinate was immediately soluble in 2N-sodium hydroxide and was precipitated unchanged if immediately acidified. It did not react with periodic acid, ozone, or 2 : 4-dinitrophenylhydrazine hydrochloride. Prepared with acetic anhydride and pyridine the *monoacetate* (VII; R = H, R′ = Me, R″ = Ac) separated from ethyl acetate–light petroleum in needles, m. p. 198—199°, $\nu_{max.}$ 3455 (OH) and 1726 cm.$^{-1}$ (CO_2Me and OAc) [Found: C, 58·8; H, 6·6; OMe, 8·7; Ac, 11·8. $C_{15}H_{13}O_5(OMe)(OAc)$ requires C, 58·7; H, 6·6; OMe, 8·4; Ac, 11·7%]. Prepared from methyl dihydro-β-picrotoxinate (1 g.) by treatment with boiling 2N-sodium hydroxide (30 ml.), *dihydro-β-picrotoxinic acid* (VII; R = R′ = R″ = H) separated from ethyl acetate in prisms (0·7 g.), m. p. 249—250° (decomp.), $\nu_{max.}$ 3425, 3485, and 1736 cm.$^{-1}$ (Found: C, 57·4; H, 6·5. $C_{15}H_{20}O_7$ requires C, 57·6; H, 6·4%). Treatment of this acid with diazomethane in ether regenerated the methyl ester, m. p. and mixed m. p. 249—250°.

Oxidation of Dihydro-β-picrotoxinic Acid with Lead Dioxide.—This acid (0·4 g.) in acetic acid (4 ml.) was treated with lead dioxide (0·4 g.) at 100° for 45 min. The excess of lead dioxide was then removed by filtration and washed with acetic acid, and the combined filtrate and washings were evaporated to dryness *in vacuo*. The solid residue was dissolved in water (30 ml.), and the *ketone* (VIII) isolated by continuous extraction in ether and purified by crystallisation from ethyl acetate, giving needles (0·19 g.), m. p. 216—217°, $\lambda_{max.}$ 302 mμ (log ε, 1·46), $\nu_{max.}$ 3427 (OH), and 1767 cm.$^{-1}$ (*cyclo*pentanone) (Found: C, 62·9; H, 6·9. $C_{14}H_{18}O_5$ requires C, 63·1; H, 6·8%). The 2 : 4-*dinitrophenylhydrazone* separated from alcohol in yellow needles, m. p. 280—289° (decomp.) (Found: C, 53·9; H, 4·9; N, 12·6. $C_{20}H_{22}O_8N_4$ requires C, 53·8; H, 4·9; N, 12·6%).

XUM

neo*Picrotoxinin Acetate* (X; R = :CMe$_2$, R′ = Ac).—(*a*) Prepared according to the method of O'Donnell *et al.*,[8] *neo*picrotoxinin acetate separated from alcohol in colourless rod-like prisms, m. p. 189—190·5°, $\nu_{max.}$ 1795 ($\beta\gamma'$-unsaturated γ-lactone), 1773 (γ-lactone), and 1736 cm.$^{-1}$ (acetate).

(*b*) Finely powdered anhydropicrotin (5 g.), suspended in acetic anhydride (25 ml.) containing anhydrous ferric chloride (0·7 g.), was kept at room temperature until a homogeneous solution was obtained (7—14 days), which was then poured into water (200 ml.) and set aside for 2 days. The precipitated *neo*picrotoxinin acetate separated from alcohol in colourless rods (3·8 g.), m. p. and mixed m. p. 189—190·5° [infrared spectrum identical with compound derived from (*a*) above] (Found: C, 61·0; H, 5·4; Ac, 13·5. Calc. for $C_{15}H_{15}O_5$·OAc: C, 61·1; H, 5·4; Ac, 12·9%).

neo*Picrotoxinin Benzoate* (X; R = :CMe$_2$, R′ = Bz).—Treatment of anhydropicrotin with benzoyl chloride according to the method of Horrmann [6] gave *neo*picrotoxinin benzoate, purified by sublimation at 240°/0·01 mm., giving needles, m. p. 249—250°, $\lambda_{max.}$ 214, 274, 282 mμ (log ε 3·78, 3·07, 2·97) $\nu_{max.}$ 1808 ($\beta\gamma'$-unsaturated γ-lactone), 1785 (γ-lactone), 1724 (benzoate), 1605 and 1595 cm.$^{-1}$ (aromatic) (Found: C, 66·5; H, 5·1. Calc. for $C_{22}H_{20}O_7$: C, 66·7; H, 5·1%).

neo*Picrotoxic Acid* (XI; R = H).—Hydrolysis of either *neo*picrotoxinin acetate or the benzoate with 3% aqueous sodium hydroxide for 30 hr. at 0°, and subsequent continuous extraction with ether of the acidified hydrolysate, gave neo*picrotoxic acid*, colourless needles, m. p. 242—245° (decomp.) (from ethyl acetate–benzene), $\nu_{max.}$ 3500 and 3270 (OH), 1765 (γ-lactone), and 1712 cm.$^{-1}$ (CO_2H) (Found: C, 57·9; H, 6·0. $C_{15}H_{18}O_7$ requires C, 58·1; H, 5·8%). Prepared with diazomethane, the *methyl ester* (XI; R = Me) separated from ethyl acetate–light petroleum in plates, m. p. 253—256°, $\nu_{max.}$ 3500 (OH), 1789 (γ-lactone), and 1738 cm.$^{-1}$ (CO_2Me) (Found: C, 59·1; H, 6·3; OMe, 9·9. $C_{16}H_{20}O_7$ requires C, 59·2; H, 6·2; OMe, 9·6%). This ester dissolved readily in cold dilute sodium hydroxide and was reprecipitated unchanged on acidification. Prepared with acetic anhydride and pyridine, the *monoacetate* separated from benzene in needles, m. p. 173—174°, $\nu_{max.}$ 3497 (OH), 1792 (γ-lactone), and 1730 cm.$^{-1}$ (CO_2Me and OAc) (Found, on a sample sublimed at 165°/0·01 mm.: C, 58·3; H, 6·0; Ac, 10·7. $C_{16}H_{19}O_6$·OAc requires C, 59·0; H, 6·0; Ac, 11·7%).

Ozonolysis of neo*Picrotoxinin Acetate.*—This compound (5 g.) in ethyl acetate (150 ml.) at −80° was treated with a slow stream of ozonised oxygen for 5 hr. Removal of the solvent *in vacuo* gave the *ozonide* which separated from alcohol in colourless needles (4·0 g.), m. p. 182—184° (decomp.) (Found: C, 53·0; H, 5·0. $C_{17}H_{18}O_{10}$ requires C, 53·4; H, 4·7%). This ozonide was stable to prolonged treatment with cold water and was decomposed slowly by boiling 2N-sulphuric acid.

The ozonide (1 g.) in ethyl acetate (100 ml.) containing Adams catalyst (0·1 g.) was agitated in hydrogen until absorption ceased (20 min.) (vol. absorbed, 75 ml.; theor., 59 ml.); the catalyst was then removed and the solution extracted with water (4 × 20 ml.). The aqueous extract was distilled in a current of steam and the distillate treated with an excess of 2 : 4-dinitrophenylhydrazine sulphate in dilute sulphuric acid. The orange precipitate was collected after 24 hr. and crystallised from alcohol, to give acetone 2 : 4-dinitrophenylhydrazone in orange needles (320 mg., 52%), m. p. and mixed m. p. 125—127°. The ethyl acetate solution (after removal of acetone in water) was dried ($MgSO_4$), the solvent evaporated *in vacuo* and the residue crystallised from ethyl acetate–light petroleum, to give colourless plates (450 mg.), m. p. 180—182° (decomp.), of the ozonolysis *product*. When dried at 140°/1 mm. these plates fell to a hygroscopic powder, m. p. 223—228° (Found, for a dried sample: C, 54·3; H, 3·9. $C_{14}H_{12}O_8$ requires C, 54·5; H, 3·9%). The infrared spectrum of the hydrated material showed bands at 3570 (hydrate water), 1812 (β-keto-γ-lactone?), 1779 (γ-lactone), 1754 (OAc) and 1701 cm.$^{-1}$ (ketonic CO?). This compound was recovered unchanged after attempted formation of a 2 : 4-dinitrophenylhydrazone whereas treatment with hydroxylamine hydrochloride and pyridine at room temperature for 2 days yielded an intractable water-soluble product which gave a ruby-red ferric reaction.

Reaction of Picrotin with Acetic Anhydride.—(*a*) Picrotin (2·3 g.), which had been reprecipitated from 2N-sodium hydroxide with hydrochloric acid, was suspended in acetic anhydride (10 ml.) containing concentrated sulphuric acid (0·15 ml.) and set aside at room temperature for 2 days. The insoluble residue was collected and recrystallised from acetic acid, to give prisms (1·1 g.), m. p. 324—326° (decomp.), identified as anhydropicrotin by mixed m. p. and infrared spectrum. Decomposition of the acetic anhydride filtrate with water

XUM

(50 ml.) gave a solid (0·6 g.) which separated from alcohol in needles (0·25 g.), m. p. 215—230°, raised to 252—254° by repeated recrystallisation and identified as picrotoxinin acetate by mixed m. p. and infrared spectrum.

(*b*) A sample of picrotin (2·3 g.), which had been precipitated as in method (*a*) and then recrystallised from methanol, was treated with acetic anhydride (10 ml.) and concentrated sulphuric acid (0·15 ml.) for 2 days at room temperature. The insoluble residue was collected and crystallised from acetic acid, to give prisms (0·4 g.), m. p. 324—326°, of anhydropicrotin. The acetic anhydride filtrate was decomposed with water (50 ml.), and the resultant precipitate collected and crystallised from alcohol, to give needles (0·9 g.), m. p. 189—190·5°, identified as *neo*picrotoxinin acetate by mixed m. p. and infrared spectrum.

Treatment of Picrotin with Benzoyl Chloride.—A solution of picrotin (2 g.) in benzoyl chloride (9 ml.) was heated under reflux for 2 hr. and set aside for 24 hr. The material which separated was collected and recrystallised from acetic acid, to give prisms (350 mg.), m. p. 324—326° (decomp.), of anhydropicrotin. The benzoyl chloride solution was then added to 2N-sodium carbonate (90 ml.), and the mixture was set aside for 4 days. The brown solid which separated was collected and crystallised from alcohol, to give needles (0·8 g.), m. p. 240—246° raised to 249—250° on sublimation at 205°/0·01 mm., and identified as *neo*picrotoxinin benzoate by mixed m. p. and infrared spectrum.

DEPARTMENT OF ORGANIC CHEMISTRY,
THE UNIVERSITY OF LIVERPOOL.

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608. *Unsymmetrical Dialkylphosphinic Acids.*

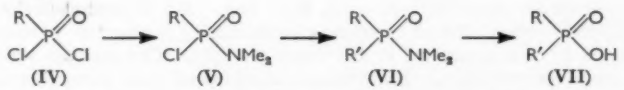
By P. C. CROFTS and I. S. FOX.

Four unsymmetrical dialkylphosphinic acids, $RR'PO_2H$, containing methyl, ethyl, *iso*propyl, and *tert.*-butyl groups have been prepared by reaction of alkylmagnesium chlorides with blocked or sterically hindered alkylphosphonic chlorides.

DERIVATIVES of phosphorus oxychloride, having one of the chlorine atoms replaced by a secondary amino-group, have previously [1] been used for the preparation of symmetrical phosphinic acids (III) by reaction of these phosphoramidic dichlorides (I) with Grignard reagents and hydrolysis of the phosphinamides (II) thus obtained:

$$POCl_3 \longrightarrow \underset{\text{(I)}}{Cl_2PO{\cdot}NR'_2} \longrightarrow \underset{\text{(II)}}{R_2PO{\cdot}NR'_2} \longrightarrow \underset{\text{(III)}}{R_2PO{\cdot}OH}$$

A similar route starting with alkylphosphonic dichlorides (IV; R = Et or Pr^i) and using Grignard reagents containing different alkyl groups has now been used to afford unsymmetrical dialkylphosphinic acids (VII; R = Et, R′ = Me; R = Et, R′ = Pr^i; R = Pr^i, R′ = Me):



(IV) (V) (VI) (VII)

The *NN*-dimethylalkylphosphonamidic chlorides (V; R = Et or Pr^i) were prepared by reaction of the alkylphosphonic dichlorides with two equivalents of dimethylamine in light petroleum. They reacted readily with alkylmagnesium chlorides in ether, to give *NN*-dimethyldialkylphosphinamides (VI; R = Et, R′ = Me; R = Et, R′ = Pr^i; R = Pr^i, R′ = Me). These were not isolated but were hydrolysed by hydrochloric acid to a mixture whence passage through a cation-exchange column and distillation afforded the phosphinic acids (VIII) as colourless liquids; ethylmethylphosphinic acid crystallised at 0°.

[1] Michaelis and Wegner, *Ber.*, 1915, **48**, 316; Kosolapoff, *J. Amer. Chem. Soc.*, 1949, **71**, 369; 1955, **77**, 6658.

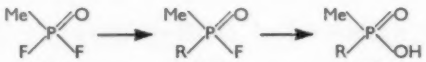
XUM

Reaction of alkylphosphonic dichlorides with alkylmagnesium halides would normally be expected to introduce two alkyl groups, forming trialkylphosphine oxides.[2] Monosubstitution has, however, been observed in reactions of this type; *tert.*-butylphosphonic with *tert.*-butylmagnesium chloride gave di-*tert.*-butylphosphinic acid,[3] a result which was ascribed to steric hindrance. It has now been found that *iso*propylmagnesium chloride reacts similarly, giving *tert.*-butyl*iso*propylphosphinic acid.

Relatively few unsymmetrical dialkylphosphinic acids have previously been described. Plets [4] reported the preparation of ethylmethylphosphinic acid (XI) by a route which involved thermal decomposition of diethylmethylphosphine dichloride (VIII) to ethylmethylphosphinous chloride (IX), and oxidation of this to ethylmethylphosphinic chloride (X), which was hydrolysed to the acid. The melting point (7—8°) of our ethylmethylphosphinic acid is however quite different from that (45—48°) of Plets's product.

$$\underset{\text{(VIII)}}{Et_2MePCl_2} \longrightarrow \underset{\text{(IX)}}{EtMePCl} \longrightarrow \underset{\text{(X)}}{EtMePO{\cdot}Cl} \longrightarrow \underset{\text{(XI)}}{EtMePO_2H}$$

Dawson and Kennard [5] recently described the preparation of three alkylmethylphosphinic acids (XIV; R = Bu^i, *n*-pentyl, *cyclo*hexyl) by reaction of alkylmagnesium halides with methylphosphonic difluoride (XII) and hydrolysis of the alkylmethylphosphinic fluorides (XIII) thus obtained. The monosubstitution in this case is a consequence of the low reactivity of the P–F bond.



(XII) (XIII) (XIV)

Experimental

Alkylphosphonic Dichlorides.—Ethylphosphonic dichloride was prepared in 71% overall yield from triethyl phosphite (100 g.) which was isomerised, by heating it with sodium iodide (1·0 g.),[6] to diethyl ethylphosphonate. After distillation, this ester was hydrolysed by refluxing hydrochloric acid. The crude ethylphosphonic acid was heated under reflux for 3 hr. with thionyl chloride, giving ethylphosphonic dichloride which was distilled.

*iso*Propyl- and *tert.*-butyl-phosphonic dichloride were prepared by hydrolysis of the complexes formed by reaction of *iso*propyl and *tert.*-butyl chloride with aluminium chloride and phosphorus trichloride.[7,3]

NN-*Dimethylethylphosphonamidic Chloride* (V; R = Et).—A solution (90 ml.) of dimethylamine (0·2 mole) in light petroleum (b. p. 30—40°) was added with stirring during 20 min. to ethylphosphonic dichloride (14·7 g.) in light petroleum (200 ml.; b. p. 30—40°). The precipitated dimethylamine hydrochloride was filtered off, and the filtrate distilled, giving NN-*dimethylethylphosphonamidic chloride* (10·5 g., 67%), b. p. 102°/10 mm. (Found: Cl, 22·1. $C_4H_{11}ONClP$ requires Cl, 22·8%).

Ethylmethylphosphinic Acid (VII; R = Et, R′ = Me).—*NN*-Dimethylethylphosphonamidic chloride (24·2 g.) in dry ether (100 ml.) was added with stirring during 2 hr. to methylmagnesium chloride (from 4·8 g. of magnesium) in dry ether (70 ml.). The mixture was heated under reflux for 4 hr. and kept overnight. Hydrochloric acid (100 ml.) and water (100 ml.) were added and the ether was distilled off. The aqueous solution remaining was evaporated, and the residue heated in hydrochloric acid (100 ml.) under reflux overnight, then evaporated, and this residue, after being kept *in vacuo* over potassium hydroxide pellets overnight was dissolved in water. The solution was passed through a cation-exchange column (Zeo-Karb 225, H form)

[2] Kosolapoff, "Organophosphorus Compounds," John Wiley & Co., New York, 1950, pp. 132—133.
[3] Crofts and Kosolapoff, *J. Amer. Chem. Soc.*, 1953, **75**, 3379.
[4] Plets, Diss., Kazan, 1938, cited in ref. 3.
[5] Dawson and Kennard, *J. Org. Chem.*, 1957, **22**, 1671.
[6] Coates and Crofts, B.P. 713,669/1954.
[7] Clay, *J. Org. Chem.*, 1951, **16**, 892; Kinnear and Perren, *J.*, 1952, 3437.

XUM

and the effluent was concentrated *in vacuo*. The yellow oil which remained was distilled, giving *ethylmethylphosphinic acid* (14·6 g., 88%). This was purified by five fractional distillations, fractions of similar refractive index being combined, and finally yielded acid (2·5 g., 15%) of b. p. 170—172°/11 mm., m. p. 7—8°, n_D^{20} 1·4514 (Found: C, 33·8; H, 7·8%; equiv., 108·9. $C_3H_9O_2P$ requires C, 33·3; H, 8·3%; equiv., 108·1).

Ethylisopropylphosphinic Acid (VII; R = Et, R′ = Pr^i).—*NN*-Dimethylethylphosphonamidic chloride (21·8 g.) in dry ether (160 ml.) was added with stirring during 30 min. to a solution of *iso*propylmagnesium chloride prepared from *iso*propyl chloride (12·8 g.) and magnesium (3·8 g.) in dry ether (140 ml.). The mixture was worked up as in the preceding experiment. The brown liquid obtained by evaporation of the effluent from the ion-exchange column was distilled three times, to give *ethylisopropylphosphinic acid* (6·0 g., 31%), b. p. 89·5°/0·017 mm., n_D^{20} 1·4567 (Found: C, 44·2; H, 9·9%; equiv., 136·7. $C_5H_{13}O_2P$ requires C, 44·1; H, 9·6%; equiv., 136·1).

NN-*Dimethylisopropylphosphonamidic Chloride* (V; R = Pr^i).—Dimethylamine (0·20 mole) and *iso*propylphosphonic dichloride (16·0 g.) in light petroleum gave, as above, NN-*dimethylisopropylphosphonamidic chloride* (13·2 g., 78%), b. p. 104°/12 mm., n_D^{25} 1·4628 (Found: Cl, 21·2. $C_5H_{13}ONClP$ requires Cl, 21·0%).

Methylisopropylphosphinic Acid (VII; R = Pr^i, R′ = Me).—*NN*-Dimethyl*iso*propylphosphonamidic chloride (17·0 g.) in dry ether (90 ml.) was added with stirring during 20 min. to methylmagnesium chloride (from 2·4 g. of magnesium) in ether (200 ml.). The mixture was heated for 2 hr. and worked up as in the preparation of ethylmethylphosphinic acid. Distillation of the residue left after evaporation of the effluent from the ion-exchange column gave *methylisopropylphosphinic acid* (7·0 g., 58%), b. p. 96—98°/0·05 mm., n_D^{24} 1·4502 (Found: C, 39·5; H, 9·2. $C_4H_{11}O_2P$ requires C, 39·3; H, 9·0%).

tert.-*Butylisopropylphosphinic Acid.*—*tert.*-Butylphosphonic dichloride (17·0 g.) in dry ether (100 ml.) was added with stirring during 30 min. to *iso*propylmagnesium chloride [from *iso*propyl chloride (10·0 g.) and magnesium (2·4 g.)] in ether (150 ml.). There was a vigorous reaction and a large amount of pale grey solid was precipitated. After being kept overnight the mixture was poured on ice (100 g.) and hydrochloric acid (2 ml.), and the ethereal layer was separated and evaporated. The resulting yellow oil was heated in ethanol (60 ml.) and hydrochloric acid (50 ml.) for 10 hr., then evaporated, leaving an oil which was dissolved in water. Charcoal and Celite were added to the solution which was then boiled, allowed to cool, filtered, and evaporated to *ca.* 40 ml. The *phosphinic acid* separated as an oil from the hot solution and crystallised on cooling. It was filtered off (0·8 g.; m. p. 73—78°). Continued evaporation of the solution gave a further 1·9 g. of the acid. The two crops were combined and recrystallised five times from light petroleum (b. p. 40—60°), to give 0·8 g. (5%) of colourless crystals, m. p. 82—84° (Found: C, 51·5; H, 10·4; P, 18·5. $C_7H_{17}O_2P$ requires C, 51·2; H, 10·4; P, 18·8%).

We are grateful to Mr. V. Manohin for the microanalyses.

MANCHESTER COLLEGE OF SCIENCE AND TECHNOLOGY
MANCHESTER, 1.

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XUM

609. *Submicro-methods for the Analysis of Organic Compounds. Part IV.* The Determination of Iodine and Bromine.*

By R. Belcher, R. A. Shah, and T. S. West.

Bromine or iodine in organic compounds is determined by decomposing a 50 μg. sample in a sealed tube with molten metallic sodium. The iodide is oxidised with bromine-water to iodate and bromide is oxidised to bromate with hypochlorite; the determinations are completed iodometrically. The sharpness of the end-point and the amplification thus achieved yield results accurate to about ±0·4% absolute.

Bromine and iodine in organic compounds are generally determined through the formation of iodate or bromate, since a six-fold amplification of the original bromine or iodine is thus obtained. Several procedures are available for decomposition of the organic compounds, but of two widely used procedures, *viz.*, combustion in a stream of air or oxygen, and fusion in a bomb with peroxide or metallic sodium, the latter was selected; absorption of microgram amounts of vapour by a small amount of liquid from a gas stream is difficult and the bomb technique eliminates possible loss of material by effecting both mineralisation and absorption in one sealed vessel.

Initially we explored both the peroxide and the sodium-fusion technique, specially designed metal bombs made from pure nickel being used.

The relatively large amount of sodium peroxide necessary for decomposition, leading to trouble in destroying the excess and difficulty in end-point detection owing to high electrolyte concentration, and the presence of impurities in this material, led us to abandon it. Superior results were obtained by sodium-fusion except that the higher temperatures caused heavy wear of the bombs. Subsequently, it was found possible to carry out the fusion in sealed borosilicate-glass tubes. The method thus offered the advantages of (*a*) requiring no special decomposition or absorption apparatus, (*b*) avoiding large volumes of solution, and (*c*) yielding a sample solution containing low concentrations of indifferent electrolyte. The fusion procedure efficiently decomposed all the compounds we have so far examined.

Determination of Iodine and Bromine in Pure Solution.[1]—Iodine is converted from iodide into iodate by oxidation with bromine water; the iodate is determined by conversion into free iodine and titration with thiosulphate after destruction of the excess of bromine with formic acid. The excess of sulphuric acid used in the acidification must be carefully controlled to minimise "after-blueing." Bromide is oxidised to bromate at pH 6·2 by hypochlorite. The excess of hypochlorite is partly destroyed by keeping the solution at 95° for 10 min. and by subsequent addition of sodium formate. Finally, potassium iodide, sulphuric acid, and a small amount of ammonium molybdate catalyst are added whereby the bromate liberates a six-fold amount of iodine. This is then titrated as described above.

Decomposition of Organic Compounds.—The sodium was purified by Bürger's procedure.[2] Uniform lengths (7 mm. for 50 μg. samples) of the sodium wire were cut with a special tool and were carefully freed as far as possible from organic solvents to minimise the formation of colloidal carbon and unknown organic products. A fusion temperature of 350° for 15 min. gave complete recovery of iodine and yielded the colloidal carbon in a tractable form. For bromine compounds, a temperature of 350—380° was used. Temperatures much above 380° produce finely divided carbon which is difficult to filter off.

Destruction of Excess of Sodium.—In most fusion procedures, ethanol is added to ensure smooth destruction of the excess of sodium metal, but we found it advisable to destroy it

* Part III, *J.*, 1958, 2393.

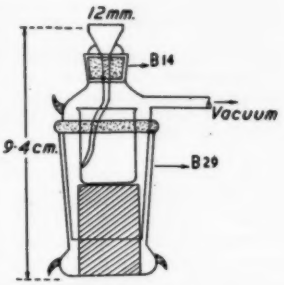
[1] See R. A. Shah, Ph.D. Thesis, Birmingham University, 1957.

[2] Burger, *Angew. Chem.*, 1941, **54**, 149; cf. also *Die Chemie*, 1942, **55**, 245; 1944, **57**, 25.

XUM

with the minimum amount of water, since this caused no risk of the formation of organic by-products which interfere in the iodometric titration.

Removal of Colloidal Carbon.—The fusion of organic compounds with metallic sodium usually produces colloidal carbon. The most particulate form was obtained within the temperature range specified; it was filtered off on paper pulp in the apparatus shown in the Figure. Failure to remove the carbon leads to errors owing to adsorption of oxidant on its surface, resulting in high consumption of hypochlorite, and obscuring of the end-point during titration. In the determination of bromine considerable amounts of hypochlorite were consumed even by the filtered solution. It is not certain whether this is caused by colloidal carbon passing through the filter or by water-soluble compounds formed during decomposition. An excess of hypochlorite considerably larger than the amount found adequate for work with pure solutions was therefore necessary to ensure complete oxidation of bromide in solutions obtained after fusion of organic bromo-compounds with sodium metal.



Determination of Iodine in Nitrogenous Compounds.—In determining iodine in nitrogen-containing compounds, cyanide formed during the fusion interfered by reacting with bromine to form cyanogen bromide which subsequently liberated iodine from potassium iodide, thus causing high recoveries. Several methods of removing cyanide were examined. The most effective involved boiling with hydrogen peroxide, with expulsion by boiling the solution just acidified with acetic acid; the latter was preferred since it is simpler and quicker. It is essential, however, that strict adherence to time, temperature, and conditions of acidity be maintained, as prolonged boiling at too high an acidity may cause serious loss of iodine as hydriodic acid. Cyanide was expelled from the fusion solution immediately after filtration. No modification of the bromine procedure was necessary for nitrogenous compounds, presumably because of the oxidation of cyanide ion by the hypochlorite.

Standardisation of Reagents.—For the determination of iodine, the thiosulphate was standardised in the normal way on the submicro-scale, a standard solution of potassium iodate being used. A similar procedure was used for bromine, but a slight tendency for low results to be obtained can be avoided by standardisation against pure potassium bromide (prepared by ignition of recrystallised potassium bromate) by oxidising it in the specified manner and taking it through the whole procedure. The improvement thus obtained is, however, slight.

Effects of Time and Temperature on the Oxidations.—Iodide is oxidised to iodate by bromine-water smoothly and rapidly at room temperature, but *ca.* 30 sec. should elapse before adding formic acid to destroy the excess of bromine. Considerably more care is needed in oxidising bromide to bromate by hypochlorite. The pH must be adjusted to *ca.* 6—6·2. It does not appear to matter whether the temperature is 90° or 95° provided that it is kept constant and that the blanks are determined at the same temperature. We controlled the temperature at 94° ± 1·0°.

The results obtained for several iodo- and bromo-compounds are given in Tables 1 and 2. With samples weighing *ca.* 50 μg. the results are generally accurate to within ±0·4% in both methods. The maximum deviation from the true analysis obtained in each series of analyses is given in col. 6. These give a true idea of the *worst* results that may be expected in using these methods, since the results reported are not selected and none was rejected. A truer picture of the accuracy is obtainable from col. 4 (average result) and col. 5 (standard deviation, " S.d."). The samples analysed range from relatively simple compounds to the more " difficult " heterocyclic materials; fluorine and chlorine do not interfere.

TABLE 1. *Analysis of iodine-containing compounds.*

Compound	Range of sample wts. (μg.)	I content (%) Calc.	Found (mean)	S.d.	No. of dtmns.	Range of errors (%) Max.	Min.
o-Iodobenzoic acid	50—56	51·17	51·14	0·17	8	+0·30	−0·02
6-Deoxy-1 : 3-2 : 4-diethylidene-6-iodo-sorbitol	52—59	36·2 *	36·2	0·33	5	−0·49	+0·08
6-Deoxy-1 : 2-3 : 4-diethylidene-5-*O*-trichloroacetyl-6-iodosorbitol	49—53	25·97	25·62	—	4	−0·41	−0·2
p-Iodoacetanilide	41—57	48·61	48·7	0·25	6	−0·41	+0·06
Phenyltrimethylammonium iodide	43—51	48·26	48·36	0·28	5	+0·44	−0·08
" Ferron "	52—56	36·14	35·97	—	3	−0·42	+0·28
1-(2-Ethylphenyl)ethyltrimethylammonium iodide	47—61	39·79	39·84	0·11	6	+0·36	−0·02
5-Iodo-2-nitrobenzotrifluoride	41—53	40·04	39·92	0·32	6	+0·37	−0·03
Methyl 2-benzyloxycarbonylamino-6-iodo-α-D-glucoside	53—56	29·04	28·87	—	4	−0·48	+0·13

* Result by routine micromethod; theory 36·9.

TABLE 2. *Analysis of bromine-containing compounds.*

Compound	Range of sample wts. (μg.)	Br content (%) Calc.	Found (mean)	S.d.	No. of dtmns.	Range of errors (%) Max.	Min.
p-Bromobenzoic acid	49—60	39·75	39·74	0·43	7	+0·46	+0·2
Bromomethyl-triphenylpyrrolone	38—62	19·78	19·71	0·19	6	−0·26	−0·01
p-Nitrobenzyl bromide	56—69	36·99	36·95	0·36	5	+0·57	−0·08
6-Deoxy-1 : 3-2 : 4-diethylidene-6-bromo-D-sorbitol	38—70	26·3 *	26·21	—	4	−0·49	−0·07
p-Bromophenacyl bromide	55—59	57·50	57·54	—	3	−0·13	+0·03
p-Bromonitrobenzene	50—60	39·56	39·56	—	4	+0·58	−0·05
β-(2-Bromo-4 : 5-dibenzyloxyphenyl)-propionamide	50—53	18·16	18·21	—	4	−0·33	−0·05

* Result by routine micromethod; theory 26·9.

EXPERIMENTAL

Determination of Iodine.—(A) *Reagents.* (1) 0·02N-Potassium iodate prepared from " AnalaR " salt. (2) 10% Aqueous potassium iodide freshly prepared daily. (3) 2N-Sulphuric acid by dilution of " M.A.R." acid. (4) 90% Formic acid, " M.A.R." (5) Bromine water (saturated) prepared from " M.A.R." bromine. (6) 0·01N-Sodium thiosulphate prepared from " AnalaR " salt and containing 100 mg. of Na_2CO_3 per l. of solution; this solution was standardised on the submicro-scale against the 0·02N-potassium iodate. (7) Sodium metal, purified by Bürger's procedure,[3] drawn into 1-mm. wire form, and stored under light petroleum (b. p. 80—100°) containing a little pentyl alcohol in a tightly stoppered bottle. (8) " Thyodene " indicator. (9) Methyl Red indicator, 0·05% aqueous.

(B) *Apparatus.*—(1) " Agla " micrometer syringe burettes, used as described previously.[3] (2) Electrically heated " Dural " block bored to hold the fusion tubes, used at 300—450°. The flat circular heating element was rated at 800 w/230 v. The block was well insulated in asbestos–cement tubing. (3) Magnetic stirrer. (4) Submicro-filtration device (see Figure). (5) Transference pipette. (6) Fusion tubes. These were made of borosilicate-glass tubing (8 mm. internal diam., 11—12 mm. outside diam., 7 cm. long) with a hemispherical seal at one end. They were cleaned with chromic acid.[3] (7) Sodium cutting tool. This was fashioned like a pair of forceps with the gap between the blades adjusted to 7 mm. (8) Submicro-balance, as described elsewhere.[4]

(C) *Recommended Procedures.*—A 50 μg. sample was weighed into the fusion tube by tapping the inverted weighing boat held in a pair of tweezers over its mouth. The boat was then reweighed. In each case the mean of three consecutive balance readings was taken. The tube was tapped gently to ensure transference of the sample to the bottom of the tube. Some sodium wire was then dried between Whatman No. 42 filter-papers, and a 7 mm. length then immersed briefly in ethanol, pressed once more between filter-papers, and put in the fusion

[3] Belcher, West, and Williams, *J.*, 1957, 4323.
[4] Asbury, Belcher, and West, *Mikrochim. Acta*, 1956, 598.

tube. The tube was held in forceps by its upper end while being sealed about 2 cm. lower down; it was then placed in the heating block for 15 min. at 350°, then removed and allowed to cool. Tubes were opened by making a scratch some 2 cm. below the point recently sealed, and placing a molten soft-glass rod against it. A micro-drop of water was placed on the walls of the opened fusion tube by means of a transference pipette. The tube was gently tapped till the water made gradual contact with the sodium. When reaction had ceased a second drop was added similarly to ensure complete destruction of the metal. 0·2 ml. of water was added and the tube was set aside for *ca.* 2 min. to permit the sodium salts to dissolve. Meanwhile a little paper pulp was placed in the filtration device and washed 5 or 6 times with distilled water. The liquid in the fusion tube was filtered carefully into a clean micro-beaker under gentle suction, a transference pipette being used to deliver the liquid to the filter funnel. When all the liquid had been filtered, 0·2 ml. of distilled water was washed down the sides of the fusion tube and the liquid again filtered. The washing was repeated four times in all with 0·2 ml. portions of water. Several more washings with 0·1 ml. portions were then done to ensure quantitative transference of the sodium salts. (A fresh filter pad was used for each determination.)

The contents of the beaker were then stirred magnetically, a drop of Methyl Red indicator added, and the solution neutralised with 2N-sulphuric acid from a syringe burette. Two drops of bromine-water were added, and after 30 sec., two drops of formic acid. After 7 minutes' more stirring, the air above the liquid in the titration beaker was pumped away to remove traces of bromine. A drop of 2N-sulphuric acid and 3 drops of 10% potassium iodide solution were added, and the liberated iodine was titrated within ½ min., standard thiosulphate and " Thyodene " indicator being used. The solid indicator was added from a micro-spatula when the yellow colour of iodine had almost vanished. A similar beaker filled to the same level with distilled water was used for comparison in locating the end-point. Lighting conditions similar to those described earlier were used.[3]

Blank (Control) Determination.—These were carried out simultaneously with the actual analyses. It was sometimes found useful to check the accuracy of the blank value by adding a known amount (say 100 µl.) of standard 0·02N-iodate to the filtered " blank " solution and comparing the recovery with the known equivalence, particularly in assessing very small blank values. A normal blank value was 2—6 µl. of 0·01N-thiosulphate.

$$1\ \mu l.\ of\ 0{\cdot}01N\text{-}Na_2S_2O_3 \equiv 0{\cdot}2115\ \mu g.\ of\ I.$$

Determination of Iodine in Nitrogenous Compounds.—Reagents and apparatus. These were as above, with the addition of 4N-acetic acid, and boiling-tubes of borosilicate glass of similar shape to fusion tubes but of 1·6 cm. diam. and having platinum ribbon (*ca.* 1 cm. long) fused through the bottom. By heating the outer end of the platinum strip with a micro-burner, heat is transferred smoothly to the liquid, thus ensuring boiling without " bumping."

Procedure. As before, but the filtrate was collected in a boiling tube (as above) instead of a 5 ml. beaker. The cyanide was removed by neutralisation to Methyl Red with 4N-acetic acid, addition of 30 µl. in excess, dilution to 3 ml., and gentle boiling as described above for 2 min. The tube was then cooled under the tap, the inner surface carefully washed with 2 or 3 drops of water, and the determination carried out as described for non-nitrogenous compounds after oxidation with bromine, etc.

N.B. If the excess of acetic acid, volume of solution, and recommended boiling time are not adhered to, there is serious danger of loss of hydriodic acid at this stage.

Blanks were determined as before.

Determination of Bromine.—Reagents. (1) 1N-Sodium hypochlorite, prepared from bromine-free sodium hypochlorite solution (14—15% available chlorine; from Imperial Chemical Industries Limited). (2) 20% Sodium dihydrogen phosphate prepared from " AnalaR " salt. (3) 50% Aqueous sodium formate. (4) 2N-Hydrochloric acid prepared by dilution of " M.A.R." acid. (5) 12N-Sulphuric acid prepared by dilution from " M.A.R." acid. (6) Ammonium molybdate solution prepared by dissolving 2·9 g. of " AnalaR " salt in 100 ml. of water. (7) Methyl Red indicator, (8) 0·01N-sodium thiosulphate, and (9) sodium metal, all as described above.

Apparatus.—As before, with the addition of an electrically heated " Dural " block to maintain the temperature of the solution at 90—95° ± 1° during oxidation of the bromide to bromate.

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Procedure.—The fusion procedure for iodine was used. The fusion tube and filter pad were tested with phenolphthalein for alkalinity to ensure complete transference and washing. The sodium hydroxide in the boiling-tube was neutralised with 2N-hydrochloric acid to a Methyl Red end-point, a micrometer syringe burette being used. The end of the burette tip was washed with 1 or 2 drops of water after removal from the liquid, the washings being collected in the tube. 300 μl. of 1N-hypochlorite and 350 μl. of sodium dihydrogen phosphate solution were then added to the tube to maintain a pH of *ca.* 6·2. The boiling-tube which now contained *ca.* 3 ml. of liquid was then placed in the heating block (temp. *ca.* 120°) for 15 min. With our apparatus, this ensured an equilibrium temperature of 94° ± 1°. Then 3 drops of 50% sodium formate solution were added, and after 30 sec. the tube was set aside for another 5 min. to cool slowly. Finally it was cooled under the tap and the sides were washed down with 3 or 4 drops of water. The tube was then mounted on the magnetic stirrer, 6 drops of 12N-sulphuric acid, 3 drops of 10% potassium iodide, and a microdrop of ammonium molybdate catalyst solution were then added, and the liberated iodine was titrated. Uniform illumination was obtained from a 60 w " daylight " blue bulb; two similar tubes containing roughly the same amount of water were used for comparison in detecting the end-point.

A usual value for the blanks is 2—3 μl. of 0·01N-thiosulphate.

Standardisation of Sodium Thiosulphate against Pure Potassium Bromide.—A slight tendency to low results can be corrected for by fusing weighed amounts of pure potassium bromide with sodium in tubes as above and carrying through the entire procedure. Pure potassium bromide can be obtained by strong ignition of doubly recrystallised " AnalaR " potassium bromate in a silica crucible. With this method of standardising the thiosulphate it is advisable to take the mean of at least six determinations; the improvement obtained is only slight.

We are grateful to Dr. J. Berger, of The Royal Danish School of Pharmacy, Copenhagen, for independently carrying out serial check determinations on both methods of analysis. One of us (R. A. S.) thanks the Commonwealth Relations Office and the Government of Pakistan for the award of a scholarship under the Colombo Plan.

CHEMISTRY DEPARTMENT, THE UNIVERSITY, BIRMINGHAM, 15. [*Received, March 3rd,* 1958.]

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610. *Molecular Polarisability. Application of the* N–H *and* N–C *Link Polarisabilities to the Conformations of Tertiary Amines, Piperidine, and Morpholine.*

By M. ARONEY and R. J. W. LE FÈVRE.

The effective longitudinal and transverse polarisabilities of the N–H and N–C bonds are deduced from measurements on ammonia and trimethylamine. In conjunction with previous results for the C–H, C–C, and C–O links, these are applied to ascertain conformations for triethylamine, piperidine, *N*-methylpiperidine, and morpholine. The three heterocycles appear to be " chair " models with N–H bonds disposed axially rather than equatorially. *N*-Methylpiperidine shows evidence that its methyl group is attached axially and equatorially with about equal frequency. The volume requirement of a " lone " electron pair on a ring nitrogen atom exceeds that of a covalently bound hydrogen atom, and seems to approach in order of magnitude that of a methyl group. Some new dipole moments are reported.

THIS work was done to determine the anisotropic polarisabilities of the N–H and N–C links, and thus to supplement analogous data [1] for C–H, C–C, and various C–hal and C–oxygen bonds. Ammonia and trimethylamine were initially selected since the geometrical specifications of their structures appeared to be satisfactorily established,[2]

[1] Le Fèvre and Le Fèvre, (*a*) *Rev. Pure Appl. Chem.*, 1955, **5**, 261; (*b*) *J.*, 1954, 1577; (*c*) *Chem. and Ind.*, 1955, 506, 1121; 1956, 54; (*d*) *J.*, 1956, 3549; (*e*) Le Fèvre, Le Fèvre, and Oh, *Austral. J. Chem.*, 1957, **10**, 218.

[2] (*a*) Herzberg, " Infrared and Raman Spectra of Polyatomic Molecules," Van Nostrand, New York, 1945, p. 439; (*b*) Brockway and Jenkins, *J. Amer. Chem. Soc.*, 1936, **58**, 2036; (*c*) Allen and Sutton, *Acta Cryst.*, 1950, **3**, 46.

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TABLE 1. *Kerr constants, dielectric polarisations, etc., of solutions in benzene at 25°.*

Solute: Ammonia

10^5w_2	301	359	368	443	456	476	483	10^5w_2	485	497
$10^{10}\Delta B$.....	10	12	14	16	16	17	17	$-10^4\Delta n$ ...	19	19

Whence $10^7\Delta B = 3{\cdot}33w_2 + 47{\cdot}9w_2^2$; $\Sigma\Delta n/\Sigma w_2 = -0{\cdot}387$.

Solute: Trimethylamine

10^5w_2	2706	5725	6202	7334	8334	9521	12,304	14,185	16,848	19,085
$-10^{10}\Delta B$	10	21	26	25	34	34	43	52	—	71
$-10^4\Delta n$	—	—	135	—	154	—	—	243	285	—

Whence $10^7\Delta B = -0{\cdot}372w_2 + 0{\cdot}021w_2^2$; $\Sigma\Delta n/\Sigma w_2 = -0{\cdot}178_4$.

Solute: Triethylamine

10^5w_2	2199	3972	6665	8913	9235	11,393	17,186	18,878
$-10^{10}\Delta B$	5	11	13	22	25	27	42	46

Whence $10^7\Delta B = -0{\cdot}243w_2 - 0{\cdot}009w_2^2$

Solute: Tri-n-propylamine

10^5w_2	867	2393	3022	3783	4178	6092	7813	9534
$-10^{10}\Delta B$	1	4	5	—	10	16	25	29
$-10^4\Delta n$	—	—	—	41	44	−65	−82	−101

Whence $10^7\Delta B = -0{\cdot}158w_2 - 1{\cdot}69w_2^2$; $\Sigma\Delta n/\Sigma w_2 = -0{\cdot}106$

10^5w_2	867	2393	3022	3783	4178	6092	7813	9534
ε^{25}	2·2734	2·2750	2·2756	—	2·2771	2·2787	—	2·2828
d_4^{25}	0·8725	0·8702	0·8693	0·8680	0·8676	0·8647	0·8625	0·8599

Whence $\Sigma\Delta\varepsilon/\Sigma w_2 = 0{\cdot}105$; $\Sigma\Delta d/\Sigma w_2 = 0{\cdot}149$

Solute: Tri-n-butylamine

10^5w_2	932	1725	2891	4136	6549	10,584
$-10^{10}\Delta B$	1	2	3	6	8	12
$-10^4\Delta n$	—	—	25	37	—	89

Whence $10^7\Delta B = -0{\cdot}134w_2 + 0{\cdot}186w_2^2$; $\Sigma\Delta n/\Sigma w_2 = -0{\cdot}086$

10^5w_2	491	932	1725	2891	4136	5447	10,584
ε^{25}	2·2730	2·2734	2·2742	2·2751	2·2768	2·2776	—
d_4^{25}	—	0·8727	0·8718	0·8704	0·8686	0·8673	0·8618

Whence $\Sigma\Delta\varepsilon/\Sigma w_2 = 0{\cdot}097$; $\Sigma\Delta d/\Sigma w_2 = -0{\cdot}135$

Solute: Tri-n-octylamine

10^5w_2	1634	2741	3903	4362	5248	5291
$-10^4\Delta n$	11	18	26	28	34	34

Whence $\Sigma\Delta n/\Sigma w_2 = -0{\cdot}065$ ($\Delta B = 0$ throughout)

10^5w_2	782	1355	2094	2538	3549	3903	5248	5291
ε^{25}	2·2729	2·2733	—	2·2738	—	2·2744	2·2747	2·2755
d_4^{25}	0·8730	0·8726	0·8719	0·8715	0·8707	0·8705	0·8690	0·8686

Whence $\Sigma\Delta\varepsilon/\Sigma w_2 = 0{\cdot}051$; $\Sigma\Delta d/\Sigma w_2 = -0{\cdot}090$

Solute: Tri-n-decylamine

10^5w_2	2269	2673	4958	6253
$-10^4\Delta n$	14	16	30	38

Whence $\Sigma\Delta n/\Sigma w_2 = -0{\cdot}061$ ($\Delta B = 0$ throughout)

10^5w_2	1281	2067	2391	3654	3823	4754
d_4^{25}	0·8727	0·8720	0·8719	0·8710	0·8706	0·8701

Whence $\Sigma\Delta d/\Sigma w_2 = -0{\cdot}082$ ($\Delta\varepsilon = 0$ throughout)

Solute: Piperidine

10^5w_2	3592	6223	8828	13,565
$-10^4\Delta n$	15	26	39	56

Whence $\Sigma\Delta n/\Sigma w_2 = -0{\cdot}0422$ ($\Delta B = 0$ throughout)

10^5w_2	1515	2679	3441	3550	5153	6649
ε^{25}	2·2990	2·3200	—	2·3347	—	—
d_4^{25}	—	—	0·87361	—	0·87351	0·87347

Whence $\Sigma\Delta\varepsilon/\Sigma w_2 = 1{\cdot}758$; $\Sigma\Delta d/\Sigma w_2 = -0{\cdot}0054$

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TABLE 1. (*Continued.*)

Solute: N-*Methylpiperidine*

10^5w_2	6519	6994	8079	8874	9656	11,467	13,224
$-10^{10}\Delta B$	29	30	35	38	41	47	58
$-10^4\Delta n$	45	—	—	62	69	—	−95

Whence $10^7\Delta B = -0{\cdot}431w_2 - 0{\cdot}0218w_2^2$; $\Sigma\Delta n/\Sigma w_2 = -0{\cdot}070$

10^5w_2	4617	6519	8079	8874	9656	13,224
ε^{25}	2·3077	2·3237	2·3356	2·3404	2·3470	2·3744
d_4^{25}	0·87065	0·86940	0·86838	0·86776	0·86735	0·86513

Whence $\Sigma\Delta\varepsilon/\Sigma w_2 = 0{\cdot}773$; $\Sigma\Delta d/\Sigma w_2 = -0{\cdot}0673$

Solute: *Morpholine*

10^5w_2	785	1332	2325	2877	3829	3963	6305	6636	8864
$-10^{10}\Delta B$	10	16	31	39	49	48	71	86	—
$10^4\Delta n$	—	—	8	10	—	15	24	—	30

Whence $10^7\Delta B = -1{\cdot}32w_2 + 1{\cdot}61w_2^2$; $\Sigma\Delta n/\Sigma w_2 = -0{\cdot}0358$

10^5w_2	1529	1726	2979	3714	3722	5392	6541
ε^{25}	2·3158	—	—	2·3802	2·3807	2·4313	2·4669
d_4^{25}	0·87563	0·87575	0·87716	0·87831	0·87820	0·88022	0·88150

Whence $\Sigma\Delta\varepsilon/\Sigma w_2 = 2{\cdot}91$; $\Sigma\Delta d/\Sigma w_2 = 0{\cdot}118$

and because (from symmetry) two semi-axes of the molecular polarisability ellipsoid in each case would be the same. Subsequently we examined six other tertiary amines, piperidine, and morpholine. Observations refer,[3] whenever possible, to the dissolved state. Results are in Table 2.

TABLE 2. *Polarisations, dipole moments, and molar Kerr constants (from observations on solutions in benzene at 25°).*

Solute	$\alpha\varepsilon_1$	β	γ	δ	M_2	$_\infty P_2$ (c.c.)	$_DP$ (c.c.)	μ (D)	$(_\infty{}_mK_2)$ $\times 10^{12}$
NH_3	11·4[a]	−0·78[a]	−0·26	8·12	17·03	46·8$_5$	5·90[b]	1·41	6·24$_5$
NMe_3	0·769[b]	−0·334[b]	−0·119	−0·907	59·12	35·4	20·2[b]	0·86	0·89$_4$
NEt_3	0·447[c]	−0·207[c]	−0·085[c]	−0·593	101·2	50·1	34·5[d]	0·87	3·8$_1$
$N(Pr^n)_3$	0·105	−0·171	−0·071	−0·385	143·3	59·9	48·7[d]	0·74	8·8$_4$
$N(Bu^n)_3$	0·097	−0·135	−0·057	−0·327	185·3	75·1	62·7[d]	0·78	11·6
$N(n\text{-}C_8H_{17})_3$	0·051	−0·103	−0·044	*ca.* 0	353·7	136·4	123·3[e]	0·80	30·2
$N(n\text{-}C_{10}H_{21})_3$	*ca.* 0	−0·094	−0·041	*ca.* 0	437·8	163·3	152·6[e]	0·72	37·7
$NH(CH_2)_5$	1·76	−0·006	−0·028	*ca.* 0	85·1	57·4	28·0[e]	1·19	1·4
$NMe(CH_2)_5$	0·773	−0·077	−0·047	−1·05	99·2	50·8	33·4[e]	0·92	−2·1
$NH(CH_2)_4O$	2·91	0·135	−0·024	−3·23	87·1	73·4	24·6[e]	1·54	−24·3

[a] Calc. from Kumler, *J. Amer. Chem. Soc.*, 1936, **58**, 1049. [b] Le Fèvre and Russell.[4] [c] Barclay, Le Fèvre, and Smythe, *Trans. Faraday Soc.*, 1950, **46**, 815. [d] Taken as R_G' from Vogel (*J.*, 1948, 1825) since no reliable measurement of $_DP$ is available. [e] *I.e.*, $1{\cdot}05R_D$. Refractions for the octyl and decyl compounds, calculated from R_G values for *n*-octane and *n*-decane (Vogel, *J.*, 1946, 133) together with appropriate bond refractions (Vogel, Cresswell, Jeffrey, and Leicester, *J.*, 1952, 514) are 119·5 and 148·0 c.c., whence $\mu = 0{\cdot}91$ and 0·87 D respectively.

Experimental.—The solvent was the remelted solid from partially frozen sodium-dried " thiophen-free benzene "; it was kept over clean sodium wire. Morpholine, piperidine, and the liquid trialkylamines (from L. Light and Co.) were dried (KOH pellets) and fractionated. Trimethylamine was prepared as in ref. 4. Ammonia was taken from a cylinder, *via* soda-lime and potassium hydroxide tubes, and directly dissolved in benzene. Solutions were made up by weight, except with ammonia: ammonia–benzene mixtures were analysed by shaking known weights with excess of standard hydrochloric acid and back-titrating with alkali (Methyl Orange). Dielectric constants were determined in the circuit noted in ref. 5; other details relating to dipole-moment estimations were as in ref. 6. Electric double refractions for sodium

[3] Ref. 1*a*, p. 298.
[4] Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43**, 374.
[5] Buckingham, Chau, Freeman, Le Fèvre, Narayana Rao, and Tardif, *J.*, 1956, 1405.
[6] Le Fèvre, " Dipole Moments," Methuen, London, 3rd Edn., 1953.

XUM

light were measured as previously described.[14,7] Extrapolations and computations were as in ref. 1*a*, pp. 281—285.

Table 1 shows, for solutions of weight fractions w_2, the differences (ΔB and Δn) between the Kerr constants and refractive indexes of the solutions and the solvent, the dielectric constants (ε) and the densities (d). Appropriate values for the pure solvent ($w_2 = 0$) are: $B_1 = 0{\cdot}410 \times 10^{-7}$, $(n_1)_D^{25} = 1{\cdot}4973$, $\varepsilon_1^{25} = 2{\cdot}2725$, and $(d_1)_4^{25} = 0{\cdot}87380$.

Discussion

(*a*) *Polarisability Ellipsoids of Ammonia and the Trialkylamines.*—The sums of the anisotropy and dipole terms, $\theta_1 + \theta_2$, are obtained[1] from the molar Kerr constants of Table 2 as ${}_\infty({}_mK_2)(9/2\pi N)$. Using the dipole moments and other quantities listed in Tables 2 and 3, we can estimate the semi-axes b_1, b_2, and b_3 without recourse to further information, provided $b_2 = b_3$ (cf. ref. 1*a*, p. 287). Such an assumption is valid for ammonia and trimethylamine, and seems reasonable for the higher members.

Table 3. *Polarisability semi-axes of ammonia and tertiary amines on the assumption that* $b_2 = b_3$.

Solute	$10^{25}(\theta_1 + \theta_2)$	${}_RP$ (c.c.)	$10^{23}(b_1 + 2b_2)$	$10^{23}b_1$	$10^{23}(b_2 = b_3)$
NH_3	$1{\cdot}48_5$	5·45 [a]	0·648	0·235	0·207
NMe_3	$0{\cdot}212_6$	19·34 [b]	$2{\cdot}299_5$	0·774	0·763
NEt_3	$0{\cdot}907_5$	32·94 [c]	3·917	$1{\cdot}33_5$	$1{\cdot}29_1$
NPr^n_3	$2{\cdot}10_2$	46·51 [c]	$5{\cdot}530_5$	$1{\cdot}93_2$	$1{\cdot}79_9$
NBu^n_3	$2{\cdot}75_5$	60·05 [c]	$7{\cdot}140_5$	$2{\cdot}48_4$	$2{\cdot}32_8$
$N(n\text{-}C_8H_{17})_3$	$7{\cdot}17_3$	117·1 [d]	13·92	$4{\cdot}870_5$	$4{\cdot}52_5$
$N(n\text{-}C_{10}H_{21})_3$	$8{\cdot}97_3$	145·0 [d]	17·24	$6{\cdot}06_2$	$5{\cdot}58_9$

[a] Watson and Ramaswamy, *Proc. Roy. Soc.*, 1936, *A*, **156**, 144. [b] Extrapolated from $R_C = 19{\cdot}791$, $R_G = 20{\cdot}406$ (cf. Vogel *et al.*, *J.*, 1952, 514. [c] Extrapolated from R_C and R_G (Vogel, *J.*, 1948, 1825). [d] *I.e.*, $0{\cdot}95({}_DP)$.

Apart from that of ammonia, the electric double refraction of none of these compounds has been examined before; dependable values exist for ammonia only as a gas.[8,9] Earlier determinations by Leiser and Hansen (quoted in ref. 1) were made relatively to carbon disulphide at unstated temperatures and wavelengths. Szivessy[8] reported the Kerr constant B as $0{\cdot}59 \times 10^{-10}$ for $\lambda = 5890$ Å at 17·9°, and Breazeale[9] gave $0{\cdot}623 \times 10^{-10}$ for $\lambda = 6550$ Å at 0° (both at 760 mm.); accordingly ${}_mK_{gas}$ is calculable as $6{\cdot}15 \times 10^{-12}$ and $6{\cdot}78 \times 10^{-12}$ respectively. These are in reasonable agreement with ${}_\infty({}_mK_2)$ now found ($6{\cdot}2_5 \times 10^{-12}$) when temperature differences are remembered; further, if μ_{gas} for ammonia be taken[4] as 1·45 D, semi-axes can be deduced as $b_1 = 0{\cdot}233 \times 10^{-23}$, $b_2 = b_3 = 0{\cdot}208 \times 10^{-23}$ (from Szivessy's B) and $b_1 = 0{\cdot}232 \times 10^{-23}$, $b_2 = b_3 = 0{\cdot}208 \times 10^{-23}$ (from Breazeale's B), and concordance exists with the results (Table 3) obtained at infinite dilution in benzene.

(b) *Polarisability Ellipsoids of the* N–H *and* N–C *Bonds.*—In both ammonia and trimethylamine the molecular resultant dipole moment and the polarisability semi-axis b_1 act through the nitrogen atom, along the three-fold axis of symmetry which is inclined at 67° 58′ to the N–H links in ammonia[2a] and at 69° 4′ to the N–C links in trimethylamine.[2b] If b_L^{N-H}, b_T^{N-H}, b_L^{C-N}, and b_T^{C-N} represent the longitudinal and transverse polarisabilities of the N–H and C–N bonds respectively, equations[10] can be set up for the (molecular) axes b_1 and for the totals ($b_L^{bond} + 2b_T^{bond}$). Thus for ammonia we have (Table 3):

$$0{\cdot}235 \times 10^{-23} = 3(b_L^{N-H} \cos^2 67° 58' + b_T^{N-H} \sin^2 67° 58')$$

and

$$0{\cdot}648 \times 10^{-23} = 3(b_L^{N-H} + 2b_T^{N-H})$$

Solution yields $b_L^{N-H} = 0{\cdot}050 \times 10^{-23}$ and $b_T^{N-H} = 0{\cdot}083 \times 10^{-23}$ c.c.

[7] Le Fèvre and Le Fèvre, *J.*, 1953, 4041; Aroney and Le Fèvre, *J.*, 1956, 2775.
[8] Szivessy, *Z. Physik*, 1924, **26**, 342.
[9] Breazeale, *Phys. Rev.*, 1935, **48**, 237.
[10] Ref. 1, pp. 297—299.

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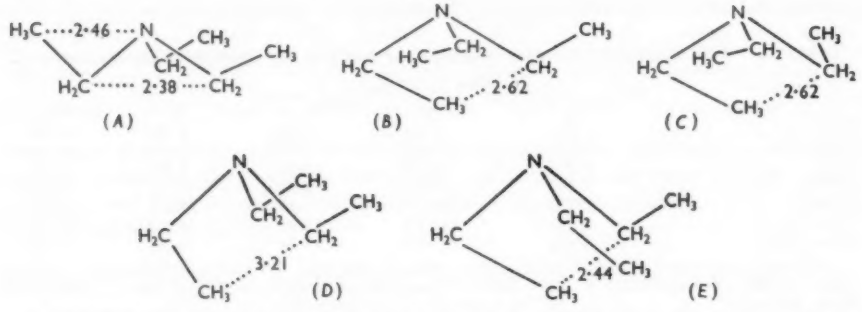
Proceeding similarly for trimethylamine, and noting [1c,10] that for the C–H bond $b_L^{C-H} = b_T^{C-H} = b_V^{C-H} = 0{\cdot}063_5 \times 10^{-23}$ c.c., we obtain values for the C–N bond: $b_L^{C-N} = 0{\cdot}057 \times 10^{-23}$ and $b_T^{C-N} = 0{\cdot}069 \times 10^{-23}$ c.c.

The N–H and C–N links are the first cases of singly-bound different atoms for which the b_T/b_L ratio exceeds unity (compare the following ratios, from ref. 1*d*: C–C 0·28, C–Cl 0·48, C–Br 0·51, C–I 0·52, C–O 0·48). Presumably, by the method of derivation, the polarisability of the " lone-pair " electrons is distributed over the three N–H or N–C bonds, so that these magnitudes do not relate entirely to the internuclear electrons. Nevertheless, such " apparent " link polarisabilities should be useful for conformational analysis of NR_3 groups containing structures in which the *s*–*p* hybridisation is likely to resemble that in ammonia and trimethylamine; examples of this kind are the subjects of the following paragraphs.

FIG. 1.



(c) *Triethylamine.*—Theoretically this base might assume an infinite number of conformations between two extremes, in both of which the three methylene and the three methyl carbon atoms are in parallel planes separated as far as permitted by the tetrahedral angles of the CH_2 groups. In one, *A* (Fig. 1), the " methyl plane " nearly includes the nitrogen atom; in the other, *F* (not shown in Fig. 1), it is most remote from it. Certain intermediate arrangements are also suggested in Fig. 1; in *C* the centres of the six carbon atoms are coplanar; in *B* five carbon atoms are coplanar but one methyl group is as in *A*; in *D* two methyl groups are as in *A* and one as in *F*; in *E* one of the methyl group is as in *A*, while the other two are located by rotating the ethyl groups containing them $\pm 120°$ respectively, about the C–N bonds, from position as in *A*. Forms *D* and *E* correspond to those suggested by Arbuzov and Guzhovina [11] (from parachor measurements) and by Brown and Taylor [12] (from kinetic and stability studies, cf. ref. 13). Intercentre distances (Å), deduced by use of C–C and C–N bond lengths of 1·54 Å and 1·47 Å and C–C–N and C–N–C angles of 109° 28′ and 108° respectively, are marked on Fig. 1, and further define the conformations. With the bond-polarisability ellipsoids given above, molecular semi-axes can be computed (Table 4) and, in turn, the molar Kerr constant to be expected for each form ($\mu_{resultant}$ being taken as 0·87 D and acting along the b_1 direction).

Measurement showed ${}_\infty({}_mK_2)$ to be $3{\cdot}8 \times 10^{-12}$, a value suggesting that none of the above forms alone occurs. Scale (Catalin) models reveal considerable steric interference between the methyl groups in conformation *F* and varying degrees of interaction between hydrogen atoms in all the other arrangements *A*—*E*. Application of the principle that the six C–H bonds of the three methylene groups should be " staggered " requires model *A* to be modified (by rotating the $-CH_2{\cdot}CH_3$ units around the N–C bonds) towards model *C*. Whether triethylamine exists as a single form intermediate between *A* and *C*, or as a

[11] Arbuzov and Guzhovina, *Doklady Akad. Nauk S.S.S.R.*, 1948, **61**, 63.
[12] Brown and Taylor, *J. Amer. Chem. Soc.*, 1947, **69**, 1332.
[13] Brown, *J.*, 1956, 1248.

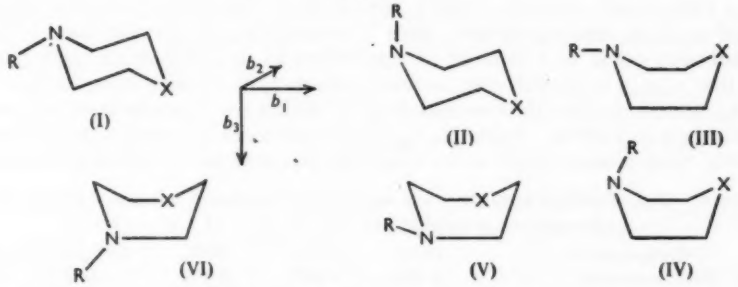
mixture of *A* and *C*, or as a state in which *A* is one limit of a libration, cannot be decided; present data are harmonious with such possibilities.

TABLE 4. *Polarisability semi-axes and molar Kerr constants calculated for conformations A to F of triethylamine.*

Conformation	$10^{23}b_1$	$10^{23}b_2$	$10^{23}b_3$	$10^{12}{}_mK_2$	Conformation	$10^{23}b_1$	$10^{23}b_2$	$10^{23}b_3$	$10^{12}{}_mK_2$
A	1·361	1·271	1·271	8·6	*D*	1·391	1·264	1·249	13·1
B	1·278	1·354	1·271	−2·9	*E*	1·308	1·332	1·263	1·1
C	1·237	1·333	1·333	−8·4	*F*	1·450	1·227	1·227	22·6

In the higher homologues, the alkyl chains do not appear to be extended " zig-zags " since on such a hypothesis the calculated b_1's fall short of those measured. If the radicals are taken as being isotropic, however, the predicted value agrees better with that observed (in parentheses) (all $\times 10^{23}$): tri-*n*-butylamine 2·5 (2·5), tri-*n*-octylamine 4·8 (4·9), tri-*n*-decylamine 5·9 (6·1). The implication is therefore that, after triethylamine, no rotational isomer predominates, and that the larger alkyl groups are " crumpled," much as their parent hydrocarbons are thought to be.[14]

FIG. 2.



(d) *Piperidine and* N-*Methylpiperidine.*—Each of these bases, if the valencies of the nitrogen atom are disposed pyramidally as in trimethylamine and the C–C–C angles are tetrahedral, can exist without ring strain as six forms: one " chair " and two " boats," for each of which in turn there are two possible conformations of the N–H (or N–Me) link. The nomenclature used with *cyclo*hexanes being used, the N–R bonds may be " equatorial " or " axial " in the chairs, and " pseudo-equatorial " or " pseudo-axial " in the boats (Fig. 2; X = CH_2).

The polarisability semi-axes to be expected for the twelve structures have been computed from the bond values given above by methods detailed in ref. 1*d*. In order to pass from the *b*'s so estimated to the corresponding molar Kerr constants, the directions of action of the resultant dipole moments need to be known. In *N*-methylpiperidine this is taken as at 69° 4′ to each N–C bond (*i.e.*, as in trimethylamine). In piperidine it should be nearer the H–N than to either C–N direction. From the dipole moments [4] of ammonia and trimethylamine and the geometry of these molecules μ^{H-N} and μ^{Me-N} appear as $1{\cdot}29_6$ and $0{\cdot}80_3$ D respectively—values which, applied in the case of dimethylamine, give the observed resultant an inclination of 45° 9′ to the H–N link in the plane defined by the hydrogen and nitrogen atoms and the mid-point between the methyl groups; a similar situation is assumed to occur in piperidine. Table 5 summarises the calculations.

With piperidine, *positive* values of ${}_mK$ are forecast for two axial conformations only, while with *N*-methylpiperidine, *negative* ones are predicted for three equatorial conformations only; the signs of the observed values show that axial N–H and equatorial N–Me links must be present to noticeable extents in the two cases. Indeed, if, as seems generally

[14] Ubbelohde and McCoubrey, *Discuss. Faraday Soc.*, 1951, **10**, 94.

likely, and by analogy with *cyclo*hexane [1d] and dioxan,[15] only *chair* structures need be considered, then piperidine contains 80% or more of the axial form, while its *N*-methyl derivative consists of the two conformations in roughly a 1 : 1 ratio.

TABLE 5. *Polarisability semi-axes and molar Kerr constants calculated for the various conformations of piperidine* (R = H; X = CH_2) *and* N-*methylpiperidine* (R = Me; X = CH_2).

Conformation	$10^{23}b_1$	$10^{23}b_2$	$10^{23}b_3$	$10^{12}{}_mK_2$	$10^{23}b_1$	$10^{23}b_2$	$10^{23}b_3$	$10^{12}{}_mK_2$
	Piperidine, $_\infty({}_mK_2) = 1{\cdot}4 \times 10^{-12}$				*N-Methylpiperidine*, $_\infty({}_mK_2) = -2{\cdot}1 \times 10^{-12}$			
(I) Chair, equatorial R ...	1·090	1·045	$0{\cdot}989_5$	−8·1	1·285	$1{\cdot}221_5$	1·169	−7·4
(II) ,, axial R	1·118	1·045	0·961	+1·9	1·295	$1{\cdot}221_5$	1·159	+8·0
(III) Boat, ψ-equatorial R	1·088	1·045	0·992	−0·9	1·286	1·221	1·168	−5·7
(IV) ,, ψ-axial R	$1{\cdot}116_5$	1·045	0·963	+12·8	1·296	1·221	1·158	+10·6
(V) ,, * ψ-equatorial R	1·044	1·078	1·003	−5·0	$1{\cdot}222_5$	1·269	1·184	−4·9
(VI) ,, * ψ-axial R	1·044	1·100	0·981	−2·6	$1{\cdot}222_5$	1·276	1·176	+3·6

* Basal nitrogen atom.

(e) *Morpholine.*—Fig. 2 shows the six models expected (X = O). The dipole moments expected for these, deduced from the N–H and N–C bond polarities used above, together with $\mu^{OH_a-O} = 1{\cdot}05$ D and ∠C–O–C = 111°, are given in Table 6. Since the moment as measured is $1{\cdot}5_4$ D, none of the four " boat " structures can be present alone. The likelihood that they occur as a mixture or equilibrium is also very small, since calculation reveals that $\mu_{resultant}$ is, in each case, inclined towards b_1 at an angle close to that [16] which makes θ_2 *ca.* zero, so that the corresponding $_mK$ differs considerably from that observed. The details are in Table 6. Since $_\infty({}_mK_2)$ from experiment is $-24{\cdot}3 \times 10^{-12}$, morpholine apparently exists almost wholly as the chair structure with the N–H link attached axially.

TABLE 6. *Polarisability semi-axes and molar Kerr constants calculated for the various conformations of morpholine* (*Fig.* 2, R = H; X = O).

Conformation	$10^{23}b_1$	$10^{23}b_2$	$10^{23}b_3$	$10^{12}{}_mK_2$	μ(D) (calc).
(I) Chair, equatorial	0·973	$0{\cdot}902_5$	0·879	+19·2	1·51
(II) ,, axial	1·002	$0{\cdot}902_5$	0·851	−25·5	1·51
(III) Boat, ψ-equatorial	0·978	0·902	0·875	−0·4	2·4
(IV) ,, ψ-axial	1·006	0·902	0·846	+0·3	0·6
(V) ,, * ψ-equatorial	0·908	0·955	$0{\cdot}892_5$	−0·1	2·0
(VI) ,, * ψ-axial	0·908	0·977	$0{\cdot}870_5$	−0·9	0·7

* Basal nitrogen atom.

The above results amplify the recognition [17] that the occurrence of *axial* N–H bonds in piperidine and morpholine was in accord with previous predictions, based on analogies with carbanions.[18] Although we [17] concluded that if ideas current in *cyclo*hexane stereochemistry can be used with heterocycles, the volume requirement of a " lone " electron pair appears to exceed that of a covalently attached hydrogen atom, *N*-methylpiperidine indicates that it approaches, in order of magnitude, that of a methyl group.

Previous Determinations of Dipole Moments.—Of our seven determinations of dipole moments recorded μ (D), four are repetitions of other work, the solvent being benzene: Tri-*n*-propylamine 0·74 (0·75 [19]), piperidine 1·19 (1·17 ± 0·02 [20]), *N*-methylpiperidine 0·92 (0·91 ± 0·01 [20]), morpholine 1·54 (1·48,[21] 1·58,[22] 1·51 [23]).

UNIVERSITY OF SYDNEY,
N.S.W., AUSTRALIA.

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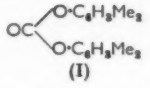
[15] Armstrong, Le Fèvre, and Yates, *Austral. J. Chem.*, 1958, **11**, 147.
[16] Ref. 1*a*, p. 294.
[17] Aroney and Le Fèvre, *Proc. Chem. Soc.*, 1958, 82.
[18] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 72.
[19] Cowley, *J.*, 1952, 3557.
[20] Rau and Narayanaswamy, *Z. phys. Chem.*, 1934, *B*, **26**, 23.
[21] Coomber and Partington, *Nature*, 1938, **141**, 918.
[22] Lewis and Smyth, *J. Amer. Chem. Soc.*, 1939, **61**, 3067.
[23] Maryott, Hobbs, and Gross, *ibid.*, 1940, **62**, 2320.

611. *Condensations of the Xylenols with Carbon Tetrahalides.*

By J. E. Driver and (Miss) T. F. Lai.

Each of the xylenols has been condensed with carbon tetrachloride by the use of zinc chloride or aluminium chloride as catalyst. Depending on the nuclear positions open to electrophilic attack varying products were obtained, namely xylyl carbonates, xylyl hydroxydimethylbenzoates, dihydroxytetramethylbenzophenones, tetramethylxanthones, aurin-type dyes, and trihydroxytrixylylmethanes. In some reactions the use of carbon tetrabromide gave increased yields of certain products.

The condensation of phenol with carbon tetrachloride [1] was found by Gomberg and Snow [2] to be complex, giving rise to a variety of products by *ortho*- and *para*-substitutions and by presumed reactions of mutual oxidation and reduction. The xylenols were selected for study because of the varying possibilities of electrophilic attack. Isolated products from xylenols and carbon tetrahalides were xylyl carbonates (I), xylyl hydroxydimethylbenzoates (II), dihydroxytetramethylbenzophenones (III), tetramethylxanthones (IV), aurin-type dyes (V), and trihydroxytrixylylmethanes (VI). These can all be traced from hypothetical dixylyloxydichloro- or trihydroxytrixylylchloro-methanes, and they give a picture of these condensations which is different from, and simpler than, that given by Gomberg and Snow for phenol.[2,3]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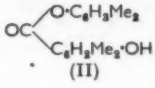
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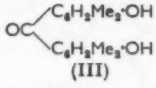
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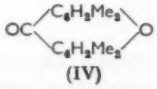
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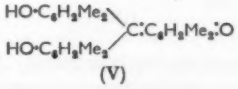
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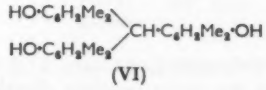
(VI)

2 : 6-Xylenol, with only the *para*-position open to attack, presents the simplest problem. With carbon tetrachloride it gave deep red 3 : 3′ : 3″ : 5 : 5′ : 5″-hexamethylaurin (VII) in high yield. The aurin gave on acetylation the diacetoxymethylenequinone (VIII) and on benzoylation the corresponding dibenzoyloxy-derivative both of which, with suppressed resonance, are yellow; aurin itself and the homologues previously acylated (" rosolic acid " and " *o*-cresaurin ") give only triacyl derivatives of the corresponding carbinols, but 3 : 3′ : 3″ : 5 : 5′ : 5″-hexabromoaurin gives a yellow diacetyl derivative as an intermediate: [4] this is therefore a steric phenomenon. Reduction of the ketone diacetate (VIII) gave the colourless phenolic diacetyl derivative (IX) which was further acetylated to the triacetyl derivative (X); this was also prepared by reduction of the dye to the *leuco*-compound (XI) and subsequent acetylation.

The structure of the aurin (VII) was confirmed by oxidation by hydrogen peroxide to 4 : 4′-dihydroxy-3 : 3′ : 5 : 5′-tetramethylbenzophenone, which by Clemmensen reduction gave the known 4 : 4′-dihydroxy-3 : 3′ : 5 : 5′-dixylylmethane.

2 : 3-Xylenol gave 2 : 2′ : 2″ : 3 : 3′ : 3″-hexamethylaurin, 2 : 3 : 2′ : 3′-dixylyl carbonate, and two yellow dihydroxytetramethylbenzophenones; one of these was shown to be the 2 : 2′-dihydroxy-3 : 3′ : 4 : 4′-tetramethyl compound by an unusual cyclization to 3 : 4 : 5 : 6-tetramethylxanthone by alkali. 2 : 5-Xylenol gave 2 : 2′ : 2″ : 5 : 5′ : 5″-hexamethylaurin [which, like (I), formed a yellow diacetyl derivative] and two crystalline substances—one (from analytical results, probably a dihydroxytetramethylbenzophenone)

[1] Friedel, *Bull. Soc. chim. France*, 1888, **50**, 2.
[2] Gomberg and Snow, *J. Amer. Chem. Soc.*, 1925, **47**, 198.
[3] Cf. also Gomberg and Anderson, *ibid.*, p. 2022.
[4] Spiers, *J.*, 1924, **125**, 450.

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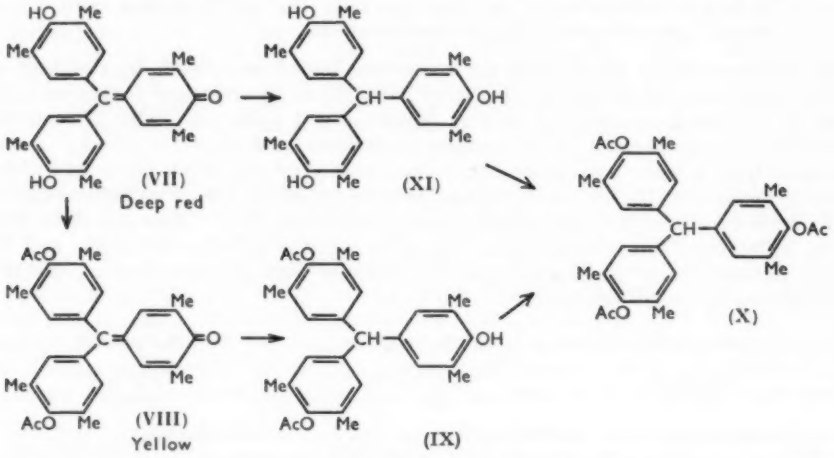
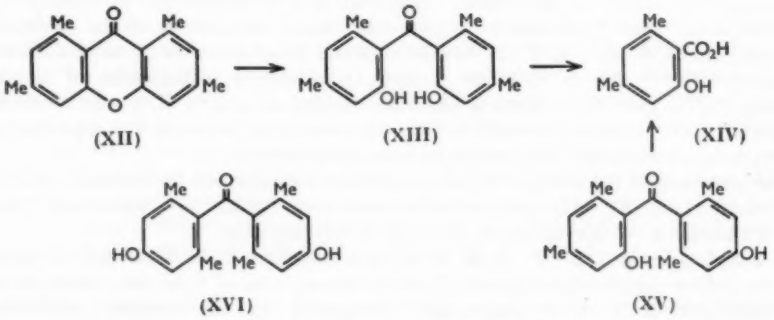
orange and soluble in 2% ammonia, the other colourless and not soluble—which were not obtained in quantity sufficient for fuller investigation.

It is interesting that **3 : 5**-xylenol, which though having a free position *para* to the hydroxyl group is there sterically hindered by the methyl groups, gave no aurin-type dye or other triphenylmethane derivative; the formation of these by the route usually depicted is impossible if formation of $CCl(C_6H_2Me_2{\cdot}OH)_3$ (or the corresponding carbinol) is prevented by steric effects. The yield of crude product in this condensation was markedly improved by the use of carbon tetrabromide, and the isolated products were **3 : 5**-xylyl 2-hydroxy-



4 : 6-dimethylbenzoate, **1 : 3 : 6 : 8**-tetramethylxanthone, **3 : 5 : 3′ : 5′**-dixylyl carbonate, and the three possible dihydroxytetramethylbenzophenones; the orientation of one of these last (XIII) was established by its formation as an intermediate degradation product of the xanthone (XII) to 2-hydroxy-**4 : 6**-dimethylbenzoic acid (XIV), that of another (XV) by formation of the same acid from it, and that of the third (XVI) by elimination (confirmed by the fact that it alone is colourless).



The two xylenols with blocked positions *para* to the hydroxyl group both yielded trihydroxytrixylylmethanes, and the same products were obtained when chloroform was used instead of the carbon tetrahalide. Reactions in which carbon tetrachloride gives the same products as chloroform have long been known.[5] Gomberg and Snow [2] obtained **4 : 4′ : 4″**-trihydroxytriphenylmethane (leucaurin) as a by-product of the condensation of

[5] Ingold and Powell, *J.*, 1921, **119**, 1222.

phenol with carbon tetrachloride, and explained it as resulting from reduction of the intermediate trihydroxytriphenylchloromethane by hydrogen provided by cyclization of a hypothetical *ortho*-substituted intermediate to a fluorone. There is no evidence of any such reactions with the xylenols (in fact, from 2 : 4-xylenol the trihydroxytrixylylmethane was the only crystalline compound isolated), and it would seem more likely that the hydrogen is provided by oxidation of simpler products to resinous complexes. 3 : 4-Xylenol yielded a trihydroxytrixylylmethane, a tetramethylxanthone, 3 : 4 : 3′ : 4′-dixylyl carbonate, and a 2 : 2′-dihydroxytetramethylbenzophenone; the last compound was shown to have methyl groups in the 4 : 6-positions, but an attempted Beckmann rearrangement of its oxime with the idea of orientating the two other methyl groups resulted in cyclization to the oxime of a tetramethylxanthone.*

In most reactions zinc chloride was employed as condensing agent, but in some aluminium chloride was found to be preferable; aluminium chloride could not however be used with 3 : 5-xylenol with which it formed a non-reactive complex. All xylenols isomerize to the 3 : 5-isomer when heated with aluminium chloride (*ca.* 2 mols.): [6] that no isomerization took place under the conditions here used (and always with less than 1 mol. of aluminium chloride) was shown by the distinct nature of the products, the fact that recovered xylenol was always the same as the original, and the results of specific experiments.

The yield of crystalline products was sometimes higher (cf., *e.g.*, above), sometimes much lower, when carbon tetrabromide was used in place of the tetrachloride; [7] it appeared that readier reaction in some cases encouraged the formation of resinous products.

The hexamethylaurins are resistant to air-oxidation in alkaline solution, as contrasted with aurin which gives 4 : 4′-dihydroxybenzophenone with ease: they will be further studied.

Experimental

Xylenols used distilled within 1°. Carbon tetrachloride and chloroform were " AnalaR." Microanalyses are by Dr. Zimmermann, Melbourne.

Condensation of 2 : 6-*Xylenol and Carbon Tetrachloride.*—A mixture of the xylenol (40 g.) and aluminium chloride (25 g.) was heated on a water-bath under reflux, and carbon tetrachloride (15·4 g.) was added dropwise. Hydrogen chloride was evolved and the mixture became red gradually. After 4 hr. water (200 ml.) was added to the viscous mass, and the excess of xylenol was removed in steam. The red solid (30 g.) was collected and washed.

The crude product, which was completely soluble in sodium hydroxide solution, was extracted with 1·5% aqueous ammonia. Acidification of the deep purple extract (temp. 60—70°) with acetic acid gave a bright red precipitate which was collected, washed, dried, and crystallized from 95% ethanol as 3 : 3′ : 3″ : 5 : 5′ : 5″-*hexamethylaurin monoethanolate*, which separated as bright red needles, m. p. 320° (decomp.) *in vacuo* (Found: C, 77·0; H, 7·7; loss at 180°/3 mm., 10·9. $C_{25}H_{26}O_3,C_2H_6O$ requires C, 77·1; H, 7·7; C_2H_6O, 10·9%). Solvent was removed at 180° under reduced pressure to give the *aurin* (Found: C, 79·8; H, 7·0. $C_{25}H_{24}O_3$ requires C, 80·2; H, 7·0%).

The *diacetyl derivative*, prepared by heating the aurin under reflux for 1 hr. with acetic anhydride and sodium acetate, separated from ethyl acetate in yellow needles, m. p. 302—304° (Found: C, 76·2; H, 6·7; Ac, 18·6. $C_{29}H_{30}O_5$ requires C, 76·0; H, 6·6; Ac, 18·8%). It was reduced by zinc and acetic acid to 4 : 4′-*diacetoxy*-4″-*hydroxy*-3 : 3′ : 3″ : 5 : 5′ : 5″-*trixylylmethane*, which separated from 95% ethanol in colourless needles, m. p. 172—174° (Found: C, 75·8; H, 7·0; Ac, 19·2%; *M*, 511. $C_{29}H_{32}O_5$ requires C, 75·6; H, 7·0; Ac, 18·7%; *M*, 461); acetylation of this yielded the triacetyl derivative, which separated from 95% ethanol in colourless, silky needles, m. p. 216—217°, mixed m. p. 217—218° with the triacetyl derivative (m. p. 218—219°) of the *leuco*-compound (below). The aurin could not be benzoylated by

* The possibility that this compound might have been the isomeric benzoxazole (cf. Meisenheimer, Hanssen, and Wächterowitz, *J. prakt. Chem.*, 1928, **119**, 315) is excluded by its properties.

[6] Baddeley, *J.*, 1943, 527.

[7] Cf. Kishore and Mathur, *J. Indian Chem. Soc.*, 1951, **28**, 72.

the Schotten–Baumann method; it was benzoylated in pyridine, to yield **4 : 4′-*dibenzoyl*-3 : 3′ : 3″ : 5 : 5′ : 5″-*hexamethylaurin*,** which separated from 95% ethanol in yellow prisms. This compound has two melting points; it melts at 169·5° when heated rapidly, and at 245—246° when heated slowly (Found: C, 79·9; H, 5·8. $C_{39}H_{34}O_5$ requires C, 80·4; H, 5·9%).

The crude product could be crystallised directly from 95% ethanol to yield the aurin. The mother-liquor then yielded crystals with a green lustre which changed to the red aurin when heated and were probably its *hydrochloride* (Found: C, 71·9; H, 6·7; Cl, 8·5. $C_{25}H_{27}O_3Cl$ requires C, 73·1; H, 6·6; Cl, 8·6%).

Oxidation. No appreciable reaction took place when oxygen was passed through an alkaline solution of the aurin for 48 hr., but oxidation was readily effected as follows. A solution of the aurin in sodium hydroxide solution was heated on a water-bath, and 3% hydrogen peroxide solution was added portionwise until the solution changed from deep red to yellow (about 3 min.). After being cooled the solution was acidified with acetic acid whereupon colourless, silky needles of **4 : 4′-*dihydroxy*-3 : 3′ : 5 : 5′-*tetramethylbenzophenone***, m. p. 223° (from aqueous ethanol), separated (Found: C, 75·5; H, 6·6. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%). The *diacetyl derivative* separated from 95% ethanol in prisms, m. p. 185—186° (Found: C, 71·3; H, 6·2; Ac, 22·2. $C_{21}H_{22}O_5$ requires C, 71·2; H, 6·3; Ac, 24·3%). The *dimethyl ether*, prepared by methyl sulphate methylation at water-bath temperature, formed prisms, m. p. 110—111°, from aqueous ethanol (Found: C, 76·2; H, 7·5; OMe, 20·7. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4; OMe, 20·8%). The *oxime* crystallized from aqueous ethanol in prisms, m. p. 230° (decomp.) (Found: C, 71·6; H, 6·7; N, 5·0%; *M*, 277. $C_{17}H_{19}O_3N$ requires C, 71·6; H, 6·7; N, 4·9%; *M*, 285). Clemmensen reduction of the ketone gave **4 : 4′**-dihydroxy-**3 : 3′ : 5 : 5′**-dixylylmethane, m. p. 173—174° (lit., 175°) (Found: C, 79·7; H, 7·8. Calc. for $C_{17}H_{20}O_2$: C, 79·7; H, 7·9%).

Reduction. The aurin was heated with zinc powder and acetic acid until the solution was almost colourless, and the excess of zinc was then removed. Dilution precipitated **4 : 4′ : 4″-*trihydroxy*-3 : 3′ : 3″ : 5 : 5′ : 5″-*trixylylmethane***, which crystallized from aqueous ethanol in needles, m. p. 220° (Found: C, 79·8; H, 7·4%; *M*, 363. $C_{25}H_{28}O_3$ requires C, 79·8; H, 7·5%; *M*, 376). The *triacetyl derivative* formed silky needles, m. p. 218—219°, from 95% ethanol (Found: C, 74·0; H, 6·9; Ac, 24·4%; *M*, 519. $C_{31}H_{34}O_6$ requires C, 74·1; H, 6·8; Ac, 25·7%; *M*, 503). The *tribenzoyl derivative*, prepared by the Schotten–Baumann method, formed silky needles, m. p. 190—191°, from 95% ethanol (Found: C, 79·7; H, 6·0. $C_{46}H_{40}O_6$ requires C, 80·2; H, 5·8%).

Condensation of **2 : 6-*Xylenol and Carbon Tetrabromide.***—The xylenol (40 g.), carbon tetrabromide (33 g.), and zinc chloride (20 g.) were heated at 100—110° under reflux. Hydrogen bromide was evolved, and after ½ hr. the excess of xylenol was removed in steam. The crude hexamethylaurin (40 g.) was completely soluble in sodium hydroxide solution and was purified as before.

Condensation of **2 : 6-*Xylenol and Chloroform.***—The xylenol (15 g.), chloroform (4·5 g.), and aluminium chloride (10 g.) were heated on a water-bath for 3 hr. After removal of xylenol the red, solid product was extracted with ether to yield **4 : 4′ : 4″**-trihydroxy-**3 : 3′ : 3″ : 5 : 5′ : 5″**-trixylylmethane, m. p. 216—218° not depressed on admixture with the reduction product of **3 : 3′ : 3″ : 5 : 5′ : 5″**-hexamethylaurin. The triacetyl derivative had m. p. 220—222°, not depressed in admixture with the triacetyl derivative of the reduction product of the aurin.

Condensation of **2 : 3-*Xylenol and Carbon Tetrachloride.***—The xylenol (30 g.), carbon tetrachloride (12 g.), and zinc chloride (15 g.) were condensed as in the first example (110—130°, 8 hr.). The crude product, a dark-brown solid (20 g.), was extracted with 5% sodium hydroxide solution; acidification with acetic acid of the deep purple extract precipitated a reddish-brown solid (15 g.) which was collected, washed, dried, and extracted (Soxhlet) with light petroleum (b. p. 60—80°). Evaporation of the extract left **2 : 2′-*dihydroxy*-3 : 3′ : 4 : 4′**-tetramethyl-***benzophenone*** which crystallized from 95% ethanol in yellow needles, m. p. 165—166° (Found: C, 75·5; H, 6·6%; *M*, 283. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%; *M*, 270). The *acetyl derivative*, crystallized from aqueous ethanol, had m. p. 129·5—130·5° (Found: C, 73·1; H, 6·5; Ac, 13·7. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·5; Ac, 13·8%). The *oxime*, made by heating the ketone with hydroxylamine hydrochloride, sodium acetate, and aqueous ethanol for 5 hr., crystallized from benzene–light petroleum in prisms which softened at 176° and melted at 180° (Found: C, 71·8; H, 6·4; N, 4·9%; *M*, 272. $C_{17}H_{19}O_3N$ requires C, 71·6; H, 6·7; N,

XUM

4·9%; *M*, 285). The ketone was boiled with 2N-sodium hydroxide for 5 hr. during which **3 : 4 : 5 : 6-*tetramethylxanthone*** separated as a white powder which crystallized from ethanol in colourless plates, m. p. 195°, and in sulphuric acid formed a yellow solution with an intense green fluorescence (Found: C, 80·6; H, 6·5%; *M*, 262. $C_{17}H_{16}O_2$ requires C, 80·9; H, 6·4%; *M*, 252).

The mother-liquor after separation of the first crop of yellow hydroxy-compound was concentrated, and addition of water then precipitated crystals which by recrystallization from aqueous ethanol yielded a yellow ***dihydroxytetramethylbenzophenone***, m. p. 184—185° (Found: C, 75·6; H, 6·8%; *M*, 270. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%; *M*, 270). The ***acetyl derivative***, crystallized from aqueous ethanol, had m. p. 127—128°, depressed to below 110° by admixture with the acetyl derivative of the compound of m. p. 165—166° (Found: C, 73·1; H, 6·6; Ac, 13·5%). The ketone did not form an oxime, and was recovered unchanged after having been heated with 2N-sodium hydroxide for 2 hr.

The alkali-soluble product, after extraction with light petroleum, was extracted with 3·5% aqueous ammonia. Acidification of the deep purple solution with acetic acid precipitated **2 : 2′ : 2″ : 3 : 3′ : 3″-*hexamethylaurin*** which separated from benzene–methanol in green needles, m. p. 297—298° (decomp.) (Found: C, 80·2; H, 7·1. $C_{28}H_{26}O_3$ requires C, 80·2; H, 7·0%). Hydrogen peroxide in alkaline solution did not oxidize the aurin, but reduction with zinc powder and acetic acid gave a product from which colourless needles (from acetic acid), m. p. 310° (decomp.), were isolated in small quantity. The acetyl derivative was difficult to crystallize and was not obtained pure.

The crude, alkali-insoluble product was extracted with light petroleum (b. p. 60—80°) (Soxhlet). The extract was washed with 5% sodium hydroxide solution, then with water, and dried (Na_2SO_4). Evaporation of solvent left crystals contaminated with resin. Short-path vacuum-distillation and crystallization from 95% ethanol yielded prisms of **2 : 3 : 2′ : 3′-*dixylyl carbonate***, m. p. 99—100·5° (Found: C, 75·5; H, 6·9. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%); this compound did not react with aniline at 150—180°/3 hr. (sealed tube, copper catalyst).

Condensation of **2 : 5-*Xylenol and Carbon Tetrachloride.***—The xylenol (50 g.), carbon tetrachloride (20 g.), and aluminium chloride (30 g.) were condensed as in the first example (120—130°, 5 hr.). From the residue a dark-brown solid (25 g.) was obtained. Extraction of this with 2% aqueous ammonia at 70—80° gave a deep violet solution which by acidification with acetic acid yielded **2 : 2′ : 2″ : 5 : 5′ : 5″-*hexamethylaurin***. This, after separation from the hot solution, crystallized from methanol in stout, red prisms, m. p. 293—295° (decomp.) (Found: C, 79·4; H, 7·1. $C_{28}H_{26}O_3$ requires C, 80·2; H, 7·0%); its alkaline solution showed no appreciable change in colour after being treated with oxygen for 50 hr., and it remained unchanged after being heated with sodium hydroxide solution and hydrogen peroxide for 2 hr. (water-bath). Reduction gave an amorphous product. The ***diacetyl derivative*** separated from 95% ethanol in yellow plates, m. p. 171—172° (Found: C, 75·8; H, 6·7; Ac, 19·0. $C_{20}H_{20}O_5$ requires C, 76·0; H, 6·6; Ac, 18·8%).

The hot filtrate after acidification of the ammonia extract yielded, on cooling, crystals, probably of a ***dihydroxytetramethylbenzophenone***, which crystallized from aqueous ethanol in orange needles, m. p. 234—238° (Found: C, 75·4; H, 6·8. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%).

The crude ammonia-insoluble product yielded colourless rods, m. p. 229—232° (decomp.), after 3 recrystallizations from aqueous ethanol (*ca.* 1 mg.).

Condensation of **3 : 5-*Xylenol and Carbon Tetrabromide.***—The xylenol (61 g.) and zinc chloride (30 g.) were heated at 120—130° under reflux, and carbon tetrabromide (55 g., in pellets) was added in 2 hr. Hydrogen bromide was evolved and the mixture became red. Heating was continued for a further hour, and the excess of xylenol was removed in steam. The mixture was stirred into water (1 l.) containing hydrochloric acid (50 ml.), and the reddish-brown resinous product (40 g.) was collected, washed, and extracted with 5% sodium hydroxide solution. The blue extract, on acidification with acetic acid, yielded a precipitate which settled to a dark resin (20 g.) which was washed and dried.

The alkali-soluble product was extracted with light petroleum (b. p. 60—80°). The hot extract deposited yellow needles when cooled (see later), and the mother-liquor, when evaporated, left a yellow crystalline mass which was recrystallized from aqueous ethanol to yield colourless plates of **3 : 5-*xylyl* 2-*hydroxy*-4 : 6-*dimethylbenzoate***, m. p. 99—100° (Found: C,

XUM

75·5; H, 6·8. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%). The *acetyl derivative* separated from methanol in hexagonal plates, m. p. 55—56° (Found: C, 73·4; H, 6·7; Ac, 14·4. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·5; Ac, 13·8%). The ester was hydrolysed by sodium hydroxide to 3 : 5-xylenol and 2-hydroxy-4 : 6-dimethylbenzoic acid, m. p. 165—166° (lit., 166°).

The alkali-soluble product after extraction with light petroleum was crystallized from dilute acetic acid (charcoal), to yield yellow crystals, which were extracted with hot benzene (see below). The residue crystallized from acetic acid as prisms, m. p. 256—260° (decomp.), which (being colourless) were 4 : 4′-*dihydroxy*-2 : 2′ : 6 : 6′-*tetramethylbenzophenone* (Found: C, 75·7; H, 6·8%; *M*, 293. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%; *M*, 270). The *diacetyl derivative* separated from light petroleum in prisms, m. p. 116—117° (Found: C, 71·5; H, 6·2; Ac, 24·2. $C_{21}H_{22}O_5$ requires C, 71·2; H, 6·3; Ac, 24·3%).

The crystals deposited from the petroleum and benzene extracts were combined, and by fractional crystallization from benzene two compounds were obtained. 2 : 2′-*Dihydroxy*-4 : 4′ : 6 : 6′-*tetramethylbenzophenone*, which was the less soluble in benzene, separated in yellow needles, m. p. 170° (Found: C, 75·5; H, 6·7%; *M*, 288. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%; *M*, 270); the *diacetyl derivative* crystallized from light petroleum in stout prisms, m. p. 120° (Found: C, 71·5; H, 6·2; Ac, 22·3. $C_{21}H_{22}O_5$ requires C, 71·2; H, 6·3; Ac, 24·3%). The ketone reacted with cold sulphuric acid, the solution changing from orange to pale yellow in a few minutes. Dilution then gave a white precipitate and a smell of 3 : 5-xylenol. The precipitate was suspended in sodium carbonate solution; after filtration, acidification precipitated 2-hydroxy-4 : 6-dimethylbenzoic acid which separated from water in needles, m. p. 164—166° undepressed on admixture with the product of hydrolysis of the xylyl 2-hydroxy-3 : 5-dimethylbenzoate. 2 : 4′-*Dihydroxy*-4 : 2′ : 6 : 6′-*tetramethylbenzophenone* separated from benzene in stout, yellow prisms, m. p. 143·5—145° (Found: C, 75·4; H, 6·7%; *M*, 284); the *diacetyl derivative* crystallized from aqueous ethanol in prisms, m. p. 127—128° (Found: C, 71·1; H, 6·2; Ac, 22·5%); the *dibenzoyl derivative*, prepared by the Schotten–Baumann method, crystallized from 95% ethanol in prisms, m. p. 187° (Found: C, 78·0; H, 5·4%; *M*, 462. $C_{31}H_{26}O_5$ requires C, 77·8; H, 5·5%; *M*, 479). This ketone likewise was decomposed by sulphuric acid with formation of 2-hydroxy-4 : 6-dimethylbenzoic acid, m. p. 164—166°.

The alkali-insoluble part of the condensation product crystallized from aqueous ethanol, to give needles which were a mixture of two compounds: these could be separated by fractional crystallization from ethanol, but were more easily separated as follows. The mixture was shaken with concentrated sulphuric acid and filtered through a sintered-glass crucible, and the filtrate was poured on crushed ice. The precipitate was collected, washed, and crystallized from 95% ethanol, to yield 1 : 3 : 6 : 8-*tetramethylxanthone*, which melted at 165—166°; its solution in concentrated sulphuric acid was yellow, with an intense green fluorescence (Found: C, 80·9; H, 6·4%; *M*, 243. $C_{17}H_{16}O_2$ requires C, 80·9; H, 6·4%; *M*, 252). The xanthone was heated with solid potassium hydroxide moistened with water, and the mixture was kept molten for 1 hr., then cooled and extracted with water. Acidification precipitated 2 : 2′-dihydroxy-4 : 4′ : 6 : 6′-tetramethylbenzophenone which crystallized from aqueous ethanol (charcoal) in yellow prisms, m. p. 170° undepressed on admixture with the ketone isolated from the xylenol condensation. The residue insoluble in sulphuric acid crystallized from aqueous ethanol as needles of 3 : 5 : 3′ : 5′-*dixylyl carbonate*, m. p. 116—117° (Found: C, 75·7; H, 6·7%; *M*, 246. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%; *M*, 270); when heated with aniline (2 mols.) and a little copper powder at 150—180° for 3 hr. (sealed tube) the carbonate yielded carbanilide, m. p. 240—241° (from aqueous ethanol) (not depressed on admixture with an authentic specimen).

Reaction of 3 : 5-*Xylenol with Aluminium Chloride.*—The xylenol (50 g.) and aluminium chloride (25 g.) were heated on a water-bath. Some hydrogen chloride was evolved and the mixture became a yellow mass which did not melt at 140°. Carbon tetrachloride was added and the mixture heated at *ca.* 140° for several hours; little reaction took place, and most of the xylenol was recovered.

The xylenol (24 g.) and aluminium chloride (13 g.) were heated in light petroleum (100 ml.) on a water-bath for 6 hr.; the white, solid residue, after being washed with light petroleum and dried, contained 11—12% of aluminium and a variable proportion (15—20%) of chlorine.

Condensation of 2 : 4-*Xylenol and Carbon Tetrachloride.*—The xylenol (40 g.), carbon tetrachloride (15·4 g.), and aluminium chloride (35 g.) were condensed as in the first example (5 hr.).

XUM

The product isolated was a brown resin (14 g.); this was digested repeatedly with 3·5% ammonia solution on a water-bath. The red ammonia extract was acidified with acetic acid, and the precipitate was washed, dried, and extracted with light petroleum (b. p. 60—80°). Removal of solvent left a yellow mass which was crystallized from aqueous ethanol to yield colourless needles of 2 : 2′ : 2″-*trihydroxy*-3 : 3′ : 3″ : 5 : 5′ : 5″-*trixylylmethane*, m. p. 145—146° (Found: C, 79·3; H, 7·7. $C_{25}H_{28}O_3$ requires C, 79·8; H, 7·5%). The *triacetyl derivative* separated from aqueous ethanol in needles, m. p. 80—82° (Found: C, 73·8; H, 7·0; Ac, 26·6. $C_{31}H_{34}O_6$ requires C, 74·1; H, 6·8; Ac, 25·7%).

No other crystalline substance was obtained from the condensation product. Condensations of the xylenol and carbon tetrabromide in the presence of aluminium chloride (90—100°, 5 hr.) or zinc chloride (110—130°, 1 hr.) yielded dark products representing up to 80% of the xylenol used, but from them no crystalline substances were isolated.

Condensation of 2 : 4-*Xylenol and Chloroform.*—The xylenol (10 g.), aluminium chloride (7 g.), and chloroform (3 g.) were condensed as in the first example (3½ hr.). The grey solid isolated was completely soluble in sodium hydroxide solution; it was soluble in light petroleum (b. p. 60—80°), and crystallized from aqueous ethanol as needles of 2 : 2′ : 2″-trihydroxy-3 : 3′ : 3″ : 5 : 5′ : 5″-trixylylmethane, m. p. 146·5—147°, mixed m. p. 146—147° with that (m. p. 145—146°) obtained in the carbon tetrachloride condensation.

Condensation of 3 : 4-*Xylenol and Carbon Tetrachloride.*—(*a*) The xylenol (92 g.), carbon tetrachloride (39 g.), and zinc chloride (20 g.) were heated at 110—130° for 24 hr. After removal of xylenol a dark-brown resin (65 g.) remained. This was extracted with 5% sodium hydroxide solution, the extract was acidified with acetic acid, and the resulting precipitate was washed, dried, and extracted with light petroleum (b. p. 60—80°). Removal of solvent left a yellow solid which separated from acetone in large crystals. These were recrystallized from benzene to yield colourless prisms of a 2 : 2′ : 2″-*trihydroxytrixylylmethane*, m. p. 163·5—164·5° (Found: C, 80·0; H, 7·8%; *M*, 371. $C_{25}H_{28}O_3$ requires C, 79·8; H, 7·5%; *M*, 376). The *triacetyl derivative* formed needles, m. p. 107—108°, from ethanol (Found: C, 74·0; H, 7·1; Ac, 25·8. $C_{31}H_{34}O_6$ requires C, 74·1; H, 6·8; Ac, 25·7%).

(*b*) The xylenol (40 g.), carbon tetrachloride (15·4 g.), and zinc chloride (30 g.) were condensed as in (*a*), but for 2½ hr. only, and the crude product (23 g.) was treated as before. The benzene recrystallization gave yellow prisms, m. p. 160—165°, depressed to 140° on admixture with the trihydroxytrixylylmethane obtained as in (*a*). Four recrystallizations from benzene raised the m. p. of this yellow 2 : 2′-*dihydroxytetramethylbenzophenone* to 166—167·5° (Found: C, 75·4; H, 6·8%; *M*, 305. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%; *M*, 270). The *diacetyl derivative* separated from 95% ethanol in long needles, m. p. 110·5—111·5° (Found: C, 71·3; H, 6·3; Ac, 23·1%; *M*, 316. $C_{21}H_{22}O_5$ requires C, 71·2; H, 6·3; Ac, 24·3%; *M*, 354). The *dibenzoyl derivative* separated from 95% ethanol in prisms, m. p. 172—172·5° (Found: C, 77·5; H, 5·4. $C_{31}H_{26}O_5$ requires C, 77·8; H, 5·5%). The *oxime*, prepared by interaction with hydroxylamine hydrochloride in aqueous ethanolic potassium hydroxide (water-bath, 2½ hr.), separated from benzene–light petroleum in prisms, m. p. 165—170° (Found: C, 71·6; H, 6·7; N, 5·3%; *M*, 291. $C_{17}H_{19}O_3N$ requires C, 71·6; H, 6·7; N, 4·9%; *M*, 285). The ketone was heated with sulphuric acid (water-bath) for several hours; dilution then precipitated 2-hydroxy-4 : 5-dimethylbenzoic acid which crystallized from aqueous ethanol in prisms, m. p. 198—200° (lit., 199°), and gave a deep violet-blue colour with ferric chloride.

To a solution of the above oxime (1 g.) in ether (15 ml.), phosphorus pentachloride (1·5 g.) was added with stirring. Removal of solvent left a brown residue which was washed, dried, and recrystallized from 95% ethanol to yield silky needles of a *tetramethylxanthone oxime*, m. p. 183°; this was insoluble in alkali, but in concentrated sulphuric acid formed a pale yellow solution with a violet-blue fluorescence (Found: C, 75·9; H, 6·4; N, 5·6. $C_{17}H_{17}O_3N$ requires C, 76·4; H, 6·4; N, 5·2%).

The alkali-insoluble part of the condensation product was extracted with light petroleum (b. p. 60—80°) (Soxhlet), and a yellow solution with a green fluorescence was obtained. On evaporation this left a dark resin which solidified. Short-path distillation *in vacuo* at 100—110° gave colourless needles of 3 : 4 : 3′ : 4′-*dixylyl carbonate*, which had m. p. 123—124° after recrystallization from 95% ethanol (Found: C, 75·7; H, 6·6. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%). By heating the carbonate with aniline (2 mols.) and a little copper powder at 150—180° for 3 hr. (sealed tube), the xylenol and carbanilide (m. p. 240—241°, not depressed on admixture with an authentic sample) were formed.

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The residue after sublimation of the carbonate was crystallized from benzene (charcoal), to yield colourless prisms of a *tetramethylxanthone*, m. p. 285—286°, which in concentrated sulphuric acid formed a yellow solution with an intense green fluorescence (Found: C, 81·2; H, 6·4. $C_{17}H_{16}O_2$ requires C, 80·9; H, 6·4%).

Condensation of 3 : 4-*Xylenol and Chloroform.*—The xylenol (8 g.), chloroform (2·6 g.), and zinc chloride (4 g.) were heated at 130—140° for 7 hr. The black solid isolated (2 g.) was extracted with 5% sodium hydroxide solution. Acidification with acetic acid and crystallization from benzene gave prisms of the 2 : 2′ : 2″-trihydroxytrixylylmethane, m. p. 162—164° not depressed on admixture with the compound obtained in the carbon tetrachloride condensation.

We are indebted to the University of Hong Kong for a research grant.

UNIVERSITY OF HONG KONG, HONG KONG. [*Received, March 17th*, 1958.

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612. *Studies in the Pyrolysis of Organic Bromides. Part XI.* The Maximally Inhibited Rate of Decomposition of* sec.-*Butyl Bromide.*

By M. N. KALE, ALLAN MACCOLL, and P. J. THOMAS.

The pyrolysis of *sec.*-butyl bromide in the presence of *cyclo*hexene, which has previously been shown to be a highly efficient chain inhibitor in bromide pyrolyses, has been found to be a first-order reaction. It shows slight inhibition. The relation of this work to that of Sergeev is discussed.

IN Part IV [1] of this series, an investigation of the dehydrobromination of *sec.*-butyl bromide in the gaseous phase was reported. It was noted that " there is a slight tendency for the rate to be less in the presence of added propene, but experimental scatter precludes quantitative conclusions." Sergeev [2] has recently reported a similar investigation, the rate constants being represented by

$$\log k_1 = 13{\cdot}04 - 45{,}500/2{\cdot}303RT$$

These Arrhenius parameters are to be compared with 12·63 and 43,800, reported in Part IV.

The temperature range investigated by Sergeev was 326—398°, to be compared with 300—350° (Part IV). In view of the possible incursion of a chain mechanism in the pyrolysis of *sec.*-butyl bromide, it was deemed desirable to repeat the investigation, using *cyclo*hexene which is much more efficient than propene [3] as an inhibitor.

EXPERIMENTAL

The apparatus, experimental technique, and calculation of rate constants were as previously described.[4] The reaction vessel, however, was of somewhat greater diameter (3″). In order to ensure that the temperature scale was identical with that used previously, and that there were no other apparatus factors, a series of some six runs with *iso*propyl bromide at each of three temperatures was carried out. The results are shown in Table 1, the calculated values being taken from the Arrhenius equation of Part III.[5] In view of the good agreement for the three temperatures, it was concluded that results obtained in the present apparatus were strictly comparable with those recorded in the earlier paper.

* Part X, *J.*, 1957, 5033.

[1] Maccoll and Thomas, *J.*, 1955, 2445.
[2] Sergeev, *Doklady Akad. Nauk S.S.S.R.*, 1956, **106**, 299.
[3] Maccoll and Thomas, *J.*, 1957, 5033.
[4] Maccoll, *J.*, 1955, 965.
[5] Maccoll and Thomas, *J.*, 1955, 979.

TABLE 1. *Values of* 10^4k_1 (*sec.*$^{-1}$).

Temp.	This work	Obs. (Pt. III)	Calc. (Pt. III)
312°	0·594	0·592	0·589
329	1·85	1·80	1·86
347	5·88	5·83	5·89

Re-investigation of the uninhibited reaction confirmed the observation [1] that the pressure increase accurately represented the degree of decomposition. A study of the temperature variation of the rate constant led to the Arrhenius equation

$$\log k_1 = 13{\cdot}179 - 45{,}400/2{\cdot}303RT$$

At the higher temperatures there is little difference between the rate constants observed in the present work and those of Part IV. However, at the lowest temperature of the range studied, the present rates are some 10% lower than those previously reported.

A number of runs were carried out in the presence of varying amounts of *cyclo*hexene. The results are shown in Table 2, p_i being the *cyclo*hexene partial pressure and p_o the initial partial pressure of the bromide.

TABLE 2. *Pyrolysis at* 318°.

p_i/p_o	0	0·05	0·2	0·4	0·8	1·2	1·9	2·2	3·0
10^4k_1 (sec.$^{-1}$)	2·52	2·53	2·29	2·37	2·18	2·21	2·38	2·37	2·28

These results show a definite, though small, decrease compared with those for the uninhibited reaction, the mean rate constant in the presence of inhibitor ($p_i/p_o > 0{\cdot}2$) being $2{\cdot}30 \times 10^{-4}$ sec.$^{-1}$, which is to be compared with the value $2{\cdot}52 \times 10^{-4}$ sec.$^{-1}$ obtained in the absence of inhibitor.

Investigation of the stoicheiometry of the reaction in the presence of added *cyclo*hexene showed that the rate of pressure increase was still a true measure of the rate of elimination of hydrogen bromide. Percentage decompositions obtained from pressure measurements are compared with those obtained by direct titration of the hydrogen bromide produced in Table 3.

TABLE 3.

Decomp. (%) (press.)	73·8	62·6	51·5	39·2	27·6	16·1
Decomp. (%) (anal.)	74·4	62·0	52·0	38·8	28·0	15·8

The first-order character was confirmed by the lack of variation of the rate constants with initial bromide pressure.

The temperature variation of the rate constants was thus investigated by measuring the rate of pressure increase in the presence of *cyclo*hexene ($p_i/p_o > 0{\cdot}2$) at a series of temperatures. The results are shown in Table 4, which includes the results of the investigation of the uninhibited reaction.

TABLE 4.

	Uninhibited reaction		Inhibited reaction			Uninhibited reaction		Inhibited reaction	
Temp.	No. of runs	10^4k_1 (sec.$^{-1}$)	No. of runs	10^4k_1 (sec.$^{-1}$)	Temp.	No. of runs	10^4k_1 (sec.$^{-1}$)	No. of runs	10^4k_1 (sec.$^{-1}$)
353·8°	4	22·3	6	20·9	318·8°	—	—	7	2·30
341·5	5	10·45	6	9·49	318·2	4	2·47	—	—
332·6	4	6·16	6	5·62	311·5	4	1·56	6	1·38
325·0	4	3·86	6	3·43	298·5	4	0·652	6	0·567

The results for the inhibited reaction fitted very well the Arrhenius equation

$$\log k_1 = 13{\cdot}530 - 46{,}470/2{\cdot}303RT.$$

DISCUSSION

The pyrolysis of *sec.*-butyl bromide in the gas phase has been shown to be a first-order homogeneous reaction leading to hydrogen bromide and butene. In the absence of inhibitors, the decomposition has been shown to contain a small chain component, which

however, can be eliminated by addition of *cyclo*hexene. This bears out our earlier contention [6] that the main factor, in the case of the bromides, determining whether the reactant can support chains is the presence of a weak C–H bond, the abstraction of hydrogen from which leads to a P radical.[5] Thus attack by a bromine atom on *sec.*-butyl bromide can lead to a P radical $CH_3 \cdot \dot{C}H \cdot CHBr \cdot CH_3$ or an S radical $CH_3 \cdot CH_2 \cdot \dot{C}Br \cdot CH_3$, and the fact that the chains do not make a very great contribution to the overall rate (about 15% at the lowest temperature studied) is no doubt connected with the fact that attack on a hydrogen atom connected to a secondary carbon atom can lead to either an S or a P radical.

The absolute rates reported in this paper are about 10% faster than those observed by Sergeev. The same discrepancy occurs in the cases of *tert.*-butyl bromide [2] and of *iso*propyl bromide.[7] The most likely explanation of the difference appears to lie in the temperature scales, a difference of one degree sufficing to account for the differences in rates in the present case.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1. [*Received, March 24th*, 1958.]

[6] Harden and Maccoll, *J.*, 1957, 5028.
[7] Semenov, Sergeev, and Kaprilova, *Doklady Akad. Nauk S.S.S.R.*, 1955, **105**, 300.

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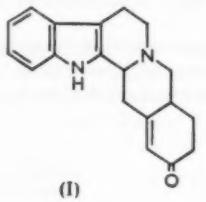
613. (±)-allo*Yohimbone and* (±)-3-epiallo*Yohimbone.*

By P. G. PHILPOTT and A. M. PARSONS.

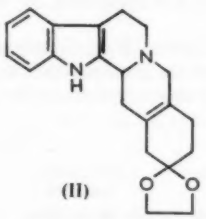
*allo*Yohimbone and 3-*epialloyo*himbone have been obtained from the ketal (II), which was prepared from the unsaturated ketone (I), an intermediate in the total synthesis of yohimbone.

SWAN [1] obtained (±)-yohimbone by hydrogenation of 2 : 3 : 4 : 4a : 5 : 7 : 8 : 13 : 13a : 14-decahydro-2-oxobenz[*g*]indolo[2 : 3-*a*]quinolizine (I) over Adams catalyst in acid solution.

In yohimbone the fusion of rings D and E is *trans*. It was hoped that by suitable change of experimental conditions a *cis*-ring junction could be obtained. du Feu, McQuillin,



(I)



(II)

and Robinson [2] obtained *cis*-β-decalone by hydrogenation of 2 : 3 : 4 : 5 : 6 : 7 : 8 : 10-octahydro-2-oxonaphthalene over palladised strontium carbonate, but in spite of the relatively close analogy only (±)-yohimbone was obtained when the compound (I) was reduced under these mild conditions.

Cornforth *et al.*[3] have shown that preparation of the ethylene ketal of 5 : 6 : 7 : 9 : 10 : 13-hexahydro-1-methoxy-13-methyl-7-oxophenanthrene (involving migration of the double bond) followed by reduction invariably gave a *cis*-ring junction. The ethylene ketal of ketone (I) was therefore prepared and its hydrogenation investigated. It was suspected that the double bond had migrated to the bridgehead because it proved rather difficult

[1] Swan, *J.*, 1950, 1534.
[2] du Feu, McQuillin, and Robinson, *J.*, 1937, 53.
[3] Cornforth, Kauder, Pike, and Robinson, *J.*, 1955, 3348.

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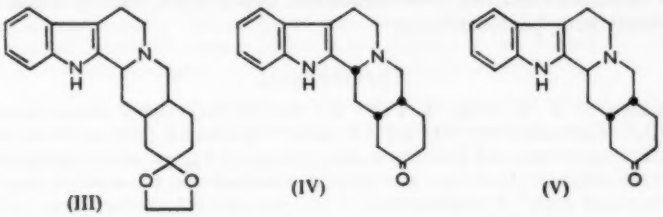
to reduce. However, by use of palladised charcoal in dioxan at elevated temperature and pressure the saturated ketal (III) was obtained smoothly and in good yield.



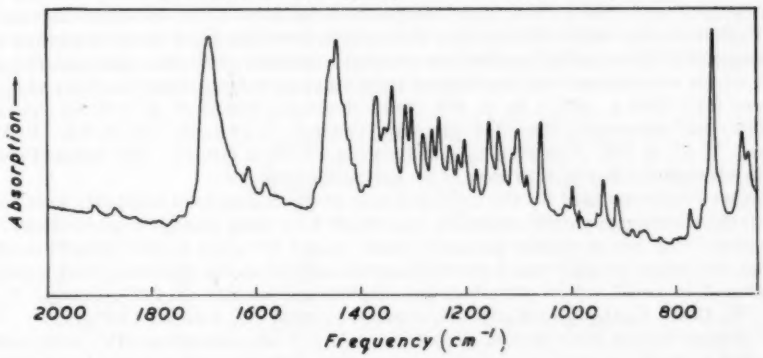
(III) (IV) (V)

In support of formula (II), comparison of infrared spectra with that of the reduced ketal (III) revealed little change in the region 1700—1600 cm.$^{-1}$ where an absorption band due to a trisubstituted double bond would normally occur. This result is surprising, for in an analogous decahydrophenanthrene derivative ketal formation is reported not to give a double bond of the tetrasubstituted type in a main product.[4]

Hydrolysis of the ketal (III) gave a ketone (IV) isomeric, but not identical, with (±)-yohimbone. The infrared spectrum agreed in all essential bands with that given for (−)-*allo*yohimbone by Le Hir, Janot, and Goutarel [5] and had some important differences from that of (±)-yohimbone.

Structure (IV) was confirmed by using the observation that under certain conditions [6] mercuric acetate reacts with compounds of this type containing an axial hydrogen atom at $C_{(3)}$. Our ketone reacted with mercuric acetate, as did yohimbine, whilst reserpine did not react. *allo*Yohimbone is the only stereoisomer of yohimbone which would be expected to give this reaction.

Infrared spectrum of 3-epiallo*yohimbone in Nujol mull.*



From the *allo*yohimbone mother-liquors a third racemate was obtained which was suspected of being 3-*epiallo*yohimbone (V). Treatment of *allo*yohimbone with pivalic acid [7] gave a mixture containing about 20% of this ketone and its structure was confirmed when it was found not to react with mercuric acetate under the above conditions.

A stereoisomer of yohimbone obtained by Bader *et al.*[8] from a naturally occurring stereoisomer of yohimbine, has been assumed by Karrer and his colleagues [9] to be

[4] Birch and Smith, *J.*, 1956, 4909.
[5] Le Hir, Janot, and Goutarel, *Bull. Soc. chim. France*, 1953, 1027.
[6] Weisenborn and Diassi, *J. Amer. Chem. Soc.*, 1956, **78**, 2022.
[7] Cf. Woodward, Bader, Bickel, Frey, and Kierstead, *ibid.*, p. 2023.
[8] Bader, Dickel, Lucas, and Schlittler, *Experientia*, 1954, **10**, 298.
[9] Vamvacas, Philipsborn, Schlittler, Schmid, and Karrer, *Helv. Chim. Acta*, 1957, **40**, 1793.

(+)-*epialloyohimbone*, but insufficient infrared data were given for a comparison with our racemate (see Figure) to be made.

3-*epialloYohimbone* did not show significant hypotensive activity when tested in a rat anæsthetised with pentobarbitone.

Experimental

Hydrogenation of 2 : 3 : 4 : 4a : 5 : 7 : 8 : 13 : 13a : 14-*Decahydro*-2-*oxobenz*[g]*indolo*[2 : 3-a]-*quinolizine* (I).[1]—Compound (I) (304 mg., 1 mmol.) in ethanol (100 c.c.) was hydrogenated at atmospheric temperature and pressure in the presence of 2% palladised strontium carbonate (100 mg.). One mmol. of hydrogen was quickly absorbed and the solution was filtered and evaporated to small bulk. Crystallisation of the precipitated product from methanol gave colourless needles of (±)-yohimbone, m. p. 265—269° (decomp.), indistinguishable from the product obtained by carrying out the reduction under the conditions used by Swan.[1]

2-*Ethylenedioxy*-1 : 2 : 3 : 4 : 5 : 7 : 8 : 13 : 13b : 14-*decahydrobenz*[g]*indolo*[2 : 3-a]*quinolizine* (II).—A mixture of 2 : 3 : 4 : 4a : 5 : 7 : 8 : 13 : 13a : 14-decahydro-2-oxobenz[g]indolo-[2 : 3-*a*]quinolizine (I) [1] (1·26 g.), toluene-*p*-sulphonic acid (1·8 g.), and ethylene glycol (20 c.c.) was heated at 100°/14 mm. under a stream of dry nitrogen for 3 hr. The solution was poured rapidly into stirred 2N-sodium carbonate (100 c.c.), and the precipitated crude ketal collected, washed with water, and dried *in vacuo*. The *product* was purified by chromatography on alumina, eluted with 1 : 1 benzene–ethyl acetate, and crystallised from ethyl acetate, to give rhombohedra (1·26 g., 87%), m. p. 238—240° (decomp.) (Found: C, 74·7; H, 7·4; N, 8·3. $C_{21}H_{24}O_2N_2$ requires C, 75·0; H, 7·1; N, 8·3%).

(±)-allo*Yohimbone* (IV).—The above ketal (4·0 g.) was hydrogenated in dry dioxan (200 c.c.) in the presence of 5% palladised charcoal (4·0 g.) at 80°/70 atm. for 17 hr. The solution was filtered and evaporated and a sample of the crude product was purified by chromatography in benzene followed by crystallisation from ethyl acetate–light petroleum (b. p. 60—80°), to give 2-*ethylenedioxy*-1 : 2 : 3 : 4 : 4a : 5 : 7 : 8 : 13 : 13b : 14 : 14a-*dodecahydrobenz*[g]*indolo*-[2 : 3-a]*quinolizine* (III), colourless rhombohedra, m. p. 198—200° (Found: N, 8·4. $C_{21}H_{26}O_2N_2$ requires N, 8·3%). The rest of the unpurified product was hydrolysed by stirring it with 2N-hydrochloric acid (200 c.c.) at room temperature for 3 hr. The resulting suspension was basified and extracted with chloroform. The residue from the dried extracts was purified by chromatography in hot ethyl acetate on alumina. Elution with the same solvent gave a product which was isolated and crystallised from ethyl acetate as rhombic plates of (±)-allo-*yohimbone* (IV) (2·88 g., 82%), m. p. 261—267° (decomp.), mixed m. p. with (±)-yohimbone [m. p. 265—269° (decomp.)], 230—255° (decomp.) (Found: C, 77·0; H, 7·5; N, 9·4. $C_{19}H_{22}ON_2$ requires C, 77·5; H, 7·5; N, 9·5%), $\lambda_{max.}$ 283 mμ (log ε 3·91) in EtOH. The infrared spectrum agrees in all essential bands with that of (−)-*allo*yohimbone.[5]

No other conditions used for the hydrogenation of the unsaturated ketal (II) were found to be satisfactory although partial reduction was effected by using Raney nickel in ethanol at 70° and 80 atm. The use of freshly prepared Raney nickel W7 gave a little dihydro-compound (III), but the major product was a perhydro-ketal isolated as the *dipicrate* which crystallised from ethanol in small yellow rhombohedra, exploding violently at 277° (Found: C, 48·9; H, 4·7; N, 13·9. $C_{21}H_{34}O_2N_2,2C_6H_3O_7N_3$ requires C, 49·2; H, 5·0; N, 13·9%).

The mother-liquors from several preparations of (±)-*allo*yohimbone (IV) were combined and yielded a small quantity of a product, m. p. 282—284° (decomp.), proved to be identical with (±)-3-*epialloyohimbone* (V) (see below).

(±)-3-epiallo*Yohimbone* (V).—A solution of (±)-*allo*yohimbone (1·0 g.) in dry xylene (100 c.c.) was heated under reflux with pivalic acid (0·8 g.) under nitrogen for 3 days. Colourless leaflets separated on chilling and these were collected and dried (0·77 g.; m. p. 265° after softening at 235°). Conversion into the free base gave almost pure (±)-*allo*yohimbone (0·60 g.). The xylene mother-liquors were evaporated to dryness under reduced pressure and the residue partitioned between 2N-sodium carbonate and chloroform. The chloroform extracts were dried, evaporated to small bulk, and chilled, and the solid was collected. Recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave (±)-3-*epialloyohimbone* (0·12 g., 12%) as elongated rhombohedra (or needles), m. p. 284—287° (decomp.), mixed m. p. with (±)-*allo*-yohimbone 243—250° (Found: C, 77·7; H, 7·3; N, 9·9. $C_{19}H_{22}ON_2$ requires C, 77·6; H, 7·5; N, 9·5%).

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Mercuric Acetate Reactions with Yohimbine, Reserpine, (±)-allo*Yohimbone and* (±)-3-epiallo*Yohimbone.*—A few mg. each of yohimbine, reserpine, (±)-*allo*yohimbone and (±)-3-*epialloy*ohimbone were added separately to equal volumes (2 c.c.) of a solution of mercuric acetate in glacial acetic acid. The solutions were kept at 60° for 2 hr., by which time there was a precipitate of mercurous acetate in the tubes containing the yohimbine and (±)-*allo*-yohimbone but not with reserpine or (±)-3-*epialloy*ohimbone, as expected.

We thank Dr. N. Sheppard of Cambridge University for help with the infrared spectra and their interpretation, and Mr. F. J. Crossley for technical assistance.

RESEARCH DEPARTMENT, ROCHE PRODUCTS LIMITED,
WELWYN GARDEN CITY, HERTS. [*Received, April 2nd,* 1958.]

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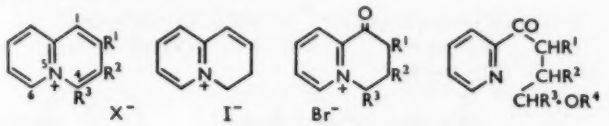
614. *Quinolizines. Part II.* A Synthesis of Alkyl- and of Aryl-quinolizinium Salts.*

By E. E. GLOVER and GURNOS JONES.

The synthesis of a number of substituted 1 : 2 : 3 : 4-tetrahydro-1-oxo-quinolizinium bromides is reported. When boiled in acetic anhydride these ketones were converted in high yield into the corresponding substituted quinolizinium salts. From the tricyclic ketones (XXVIII), (XXIX), and (XXX), by similar treatment, the three benzoquinolizinium compounds were obtained.

THE simple quinolizinium salts (I; X = I, ClO_4, and picrate) were first obtained by Boekelheide and Gall,[1] by dehydrogenation of the dihydroquinolizinium iodide (II). This method has also been successfully applied to the synthesis of 4-methylquinolizinium salts [2] (XXIV) but has failed to give 4 : 6-dimethylquinolizinium salts.[3] A second synthesis was reported by Richards and Stevens,[4] who have extended it subsequently to the preparation of a number of alkyl- and aryl-quinolizinium compounds.[5] More recently, Nesmeyanov and Rybynskaia have described a synthesis which is specific for the preparation of 2-substituted quinolizinium salts.[6]



R^1	R^2	R^3	R^4				
H	H	H	Et	(I)	(II)	(III)	(IV)
Me	H	H	Et	(XI)	—	(IX)	(VII)
Ph	H	H	Et	(XII)	—	(X)	(VIII)
H	Me	H	Me	(XIX)	—	(XVIII)	(XVII)
H	H	Me	Et	(XXIV)	—	(XXIII)	(XXII)

In a preliminary communication [7] we recorded the conversion of 1 : 2 : 3 : 4-tetrahydro-1-oxoquinolizinium bromide [8] (III) into a quinolizinium salt, isolated as quinolizinium picrate (I; X = picrate), by treatment with boiling acetic anhydride containing a drop of sulphuric acid. We now record improvements in this synthesis, together with

* Part I, *J.*, 1958, 1750.

[1] Boekelheide and Gall, *J. Amer. Chem. Soc.*, 1954, **76**, 1832.
[2] Boekelheide and Ross, *ibid.*, 1955, **77**, 5691.
[3] Personal communication from Professor Boekelheide.
[4] Richards and Stevens, *Chem. and Ind.*, 1954, 905.
[5] Richards, Ph.D. Thesis.
[6] Nesmeyanov and Rybynskaia, *Doklady Akad. Nauk S.S.S.R.*, 1957, **116**, 93.
[7] Glover and Jones, *Chem. and Ind.*, 1956, 1456.
[8] *Idem, J.*, 1958, 1750.

XUM

its extension to the preparation of 2-, 3-, and 4-substituted quinolizinium salts, and of the three types of benzoquinolizinium salts.

Earlier [7] we reported that the cyclic ketone (III), when boiled with acetic anhydride containing a trace of sulphuric acid, gave a mixture from which quinolizinium picrate (I; X = picrate) could be isolated in 63% yield. We have since found that boiling with acetic anhydride alone converts the ketone (III) into quinolizinium bromide (I; X = Br) which can be isolated in 96% yield. By this modification an overall yield of 48% has been achieved from the starting material (2-cyanopyridine). The bromide (III) was obtained by cyclization of the 2-pyridyl ketone (IV), which was prepared by Craig's method [9] from 2-cyanopyridine and 3-ethoxypropylmagnesium bromide. By suitable modification of the pyridine, or of the aliphatic precursor, a general synthesis of quinolizinium salts can be achieved. For the preparation of simple quinolizinium salts of the type (XI), (XII), (XIX), and (XXIV) we have found it most convenient to alter the aliphatic precursor.

For the preparation of 2-substituted quinolizinium salts alcohols of the type (V) or (VI) were required. These were readily obtained, in good yield, by interaction of 3-ethoxypropionaldehyde (from 3-ethoxypropionaldehyde diethyl acetal [10]) with Grignard reagents [methylmagnesium iodide gave the alcohol (V), phenylmagnesium bromide gave the analogue (VI)]. By the action of phosphorus tribromide on the alcohols (V) and (VI) the corresponding bromides were obtained, and the Grignard reagents from these bromides reacted with 2-cyanopyridine to give the pyridyl ketones (VII) and (VIII) respectively. Boiling hydrobromic acid converted these pyridyl ketones into the bromo-ketone hydrobromides; these were not isolated in a pure form but converted into the free bases by aqueous sodium carbonate. These intermediate bromo-ketones cyclized rapidly in boiling chloroform to give the oxoquinolizinium bromides (IX) and (X). The bromide (IX) was an oil which could not be obtained in a crystalline state, but both the compounds (IX) and (X) were converted in good yield into the corresponding quinolizinium salts by treatment with boiling acetic anhydride. The bromide (IX) gave 2-methylquinolizinium picrate (XI; X = picrate), and the bromide (X) gave 2-phenylquinolizinium picrate (XII; X = picrate). These picrates were converted into the perchlorates (XI; X = ClO_4) and (XII; X = ClO_4) by anionic exchange.

$HO{\cdot}CHR{\cdot}CH_2{\cdot}CH_2{\cdot}OEt$
(V): R = Me
(VI): R = Ph

$MeO_2C{\cdot}CHMe{\cdot}CH_2{\cdot}OMe$
(XIII)

$X{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}OMe$
(XIV): X = OH
(XV): X = Br
(XVI): X = Cl

(XX) $HO{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}OEt$

$EtO_2C{\cdot}CH_2{\cdot}CHMe{\cdot}OEt$ (XXI)

For the preparation of 3-substituted quinolizinium salts, alcohols such as (XIV) were required. The alcohol (XIV) was prepared in high yield by reduction of the ester (XIII), which was prepared by addition of methanol to methyl methacrylate. This addition is reported [11] to give 65% of the methyl ester (XIII) but no experimental details were given. Our yields varied from 0 to 30%, and the addition is very sensitive to changes in experimental conditions. Reduction of the ester (XIII) to the alcohol (XIV) was achieved in excellent yield by lithium aluminium hydride. Conversion of the alcohol (XIV) into the bromide (XV) was attempted but gave poor yields, and the chloride [12] (XVI) was preferred. This chloride gave a Grignard reagent which reacted with 2-cyanopyridine to form the pyridyl ketone (XVII), and this was cyclized, as described before, to the oxoquinolizinium bromide (XVIII). Boiling acetic anhydride converted the oxoquinolizinium compound (XVIII) into 3-methylquinolizinium bromide (XIX; X = Br). Since a number

[9] Craig, *J. Amer. Chem. Soc.*, 1934, **56**, 1144.
[10] Alberti and Sollazzo, *Org. Synth.*, Coll. Vol. III, p. 371.
[11] Bieber, *Compt. rend.*, 1952, **234**, 1783.
[12] Elderfield, Pitt, and Wempen, *J. Amer. Chem. Soc.*, 1955, **77**, 5691.

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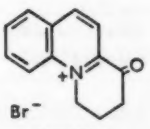
of α-substituted acrylic esters have been prepared from alkynes [13] the route outlined above should provide a general synthesis of 3-substituted quinolizinium compounds.

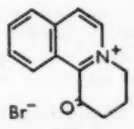
For the 4-methylquinolizinium compounds (XXIV) the aliphatic precursor was 3-ethoxybutanol (XX), obtained by reduction of ethyl β-ethoxybutyrate (XXI) with lithium aluminium hydride. The ester (XXI) was prepared [14] by addition of ethanol to ethyl crotonate in the presence of sodium ethoxide. The butanol (XX), treated with phosphorus tribromide, gave 1-bromo-3-ethoxybutane, and the Grignard reagent from this with 2-cyanopyridine gave the pyridyl ketone (XXII). For the cyclization of the pyridyl ketone (XXII) to the oxoquinolizinium bromide (XXIII) the time of boiling with 35% hydrobromic acid was kept as short as possible; prolonged boiling led to the formation of uncrystallizable oils instead of the expected crystalline bromide (XXIII). Boiling acetic anhydride converted the oxoquinolizinium compound (XXIII) into a 4-methylquinolizinium salt, isolated as the picrate (XXIV; X = picrate) agreeing in melting point and in ultraviolet absorption with that synthesized by Boekelheide and Ross.[2]

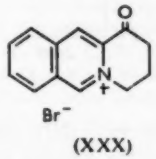
By using 2-cyanoquinoline, 1-cyano*iso*quinoline, and 3-cyano*iso*quinoline as starting materials we have synthesized the three benzoquinolizinium compounds (XXXI), (XXXII), and (XXXIII). With 3-ethoxypropylmagnesium bromide the three cyano-compounds gave the ketones (XXV), (XXVI), and (XXVII) respectively.

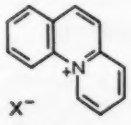
Cyclization of the quinolyl and *iso*quinolyl ketones gave the cyclic bromides (XXVIII), (XXIX), and (XXX). These were found to be less stable to traces of alkali than the oxoquinolizinium bromides (*e.g.*, III); in absolute ethanol having a very faint alkaline reaction the bromides gave dark green solutions from which no pure product could be isolated. The bromides (XXVIII) and (XXIX) were converted by boiling acetic anhydride into benzo[*c*]quinolizinium salts (XXXI) and benzo[*a*[quinolizinium salts (XXXII) respectively. The bromide (XXX), heated with acetic anhydride containing a trace of sulphuric acid, gave a benzo[*b*]quinolizinium salt, isolated as the picrate (XXXIII; X = picrate) agreeing

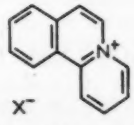
R·CO·CH_2·CH_2·CH_2·OEt
(XXV): R = 2-Quinolyl
(XXVI): R = 1-*iso*Quinolyl
(XXVII): R = 3-*iso*Quinolyl

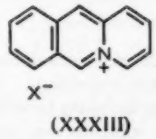

(XXVIII)


(XXIX)


(XXX)


(XXXI)


(XXXII)


(XXXIII)

in melting point with that reported by Bradsher and Beavers.[15] The same authors have reported [16] a synthesis of 7-methyl- and of 7-phenyl-benzo[*a*]quinolizinium salts, and the ultraviolet absorption of these resembles closely that of the parent benzo[*a*]quinolizinium salts prepared by us. The ultraviolet absorption spectra of the benzo[*a*]quinolizinium salts are recorded in Fig. 1 and of the benzo[*c*]quinolizinium salts in Fig. 2.

We have been unable to find an analogous synthesis in which a cyclic ketone is converted into an aromatic ring system by a " dehydration " reaction. It seems likely that the first stage is enolisation, probably with formation of the enol acetate; subsequent shift of the 1 : 2-double bond to the 2 : 3-position and 1 : 4-elimination of acetic acid gives

[13] Reppe, *Annalen*, 1953, **582**, 1.
[14] Schinz and Hinder, *Helv. Chim. Acta*, 1947, **30**, 1349.
[15] Bradsher and Beavers, *Chem. and Ind.*, 1954, 1394.
[16] *Idem*, *J. Amer. Chem. Soc.*, 1955, **77**, 453.

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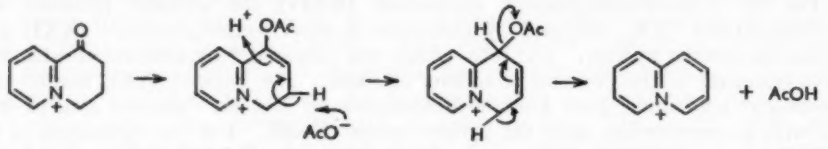
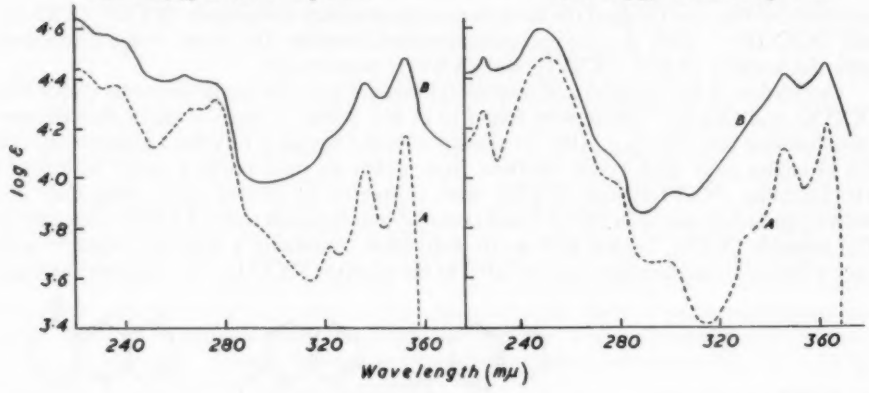
the quinolizinium cation as shown below. We have not yet performed any quantitative experiments to test this hypothesis.



[*Added June 30th*, 1958.—Prasad and Swan (*J.*, 1958, 2024) reported the synthesis of the oxo-compound (IV) and isolated as their intermediate, not the ketone (III), but the corresponding imine. We have examined compounds (IV), (XVII), and (XXVIII) with this possibility in mind, and all are free from significant infrared absorption in the

FIG. 1. *A, Benzo*[a]*quinolizinium perchlorate. B, Benzo*[a]*quinolizinium picrate.*

FIG. 2. *A, Benzo*[c]*quinolizinium perchlorate. B, Benzo*[c]*quinolizinium picrate.*



3400 cm.$^{-1}$ (NH) region; in addition, nitrogen analyses of these compounds are concordant with the ketonic structure. We conclude that under our conditions of hydrolysis the pyridyl ketones are formed, and not the imines.]

EXPERIMENTAL

M. p.s were determined on a Kofler block.

Quinolizinium Bromide (I; X = Br).—A solution of 1 : 2 : 3 : 4-tetrahydro-1-oxoquinolizinium bromide [8] (1·28 g.) in acetic anhydride (20 ml.) was boiled under reflux for 1·5 hr. The solution was cooled, the acetic anhydride hydrolysed with an equal volume of water, and the resulting solution evaporated to dryness under reduced pressure. The solid residue was precipitated from its solution in absolute ethanol by dry ether, giving quinolizinium bromide, m. p. 260—261° (1·13 g., 96%). Recrystallization from ethyl acetate–alcohol gave colourless prisms, m. p. 262—264°, $\lambda_{max.}$ 2250, 2740, 2840, 3100, 3170, 3240 Å ($\log_{10}$ ε 4·23, 3·42, 3·43, 4·00, 3·95, 4·16) in H_2O.

The picrate crystallized from absolute ethanol as yellow needles, m. p. 179° (Found: C, 50·6; H, 3·3. Calc. for $C_{15}H_{10}O_7N_4$: C, 50·3; H, 2·8%), $\lambda_{max.}$ 2270, 2850, 2880, 3120, 3190, 3250 Å ($\log_{10}$ ε 4·84, 3·64, 3·62, 4·18, 4·18, 4·4), in EtOH. A mixed m. p. with quinolizinium picrate supplied by Professor Boekelheide showed no depression. The perchlorate, obtained from the picrate by anionic exchange on Amberlite I.R.A.-400 had m. p. 287° (lit.,[1] m. p. 287°).

3-*Ethoxypropionaldehyde*.—A mixture of 3-ethoxypropionaldehyde diethyl acetal [10] (70 g.) and 3% aqueous hydrochloric acid (300 ml.) was stirred at room temperature until homogeneous. The solution was shaken several times with ether, and the ethereal solution washed with a saturated aqueous solution of calcium chloride, dried (Na_2SO_4), and distilled, giving 3-ethoxypropionaldehyde (29·5 g., 58%), b. p. 40°/16 mm.

4-Ethoxybutan-2-ol (V).—A solution of 3-ethoxypropionaldehyde (29·5 g.) in ether (50 ml.) was added dropwise to the Grignard reagent from methyl iodide (35 g.) in dry ether (400 ml.). After the addition the mixture was stirred for 1 hr., then hydrolyzed with saturated aqueous ammonium chloride. The ether layer was separated, dried (Na_2SO_4), and distilled. The yield of 4-ethoxybutan-2-ol, b. p. 69°/24 mm., n_D^{25} 1·4125, was 22·5 g. (66%).

3-Bromo-1-ethoxybutane.—Phosphorus tribromide (24 g.) was added dropwise to 4-ethoxybutan-2-ol (21 g.), the temperature being kept below 60°. The whole was then heated at 60° for 1 hr., cooled, and poured on ice, and the organic layer was washed with aqueous sodium hydrogen carbonate and with water. The crude product was dried ($MgSO_4$) and then distilled, giving 3-bromo-1-ethoxybutane, b. p. 160°/744 mm., n_D^{25} 1·4475 (22 g., 68%).

2-γ-Ethoxy-α-methylbutyrylpyridine (VII).—A stirred solution of 2-cyanopyridine (12 g.) in dry ether (100 ml.) was treated with the Grignard reagent from 3-bromo-1-ethoxybutane (21 g.) in dry ether (240 ml.), and the mixture kept overnight at room temperature. After addition of ice-cold 5N-hydrochloric acid the aqueous layer was separated and basified with aqueous ammonia (*d* 0·88), and the base extracted with ether. The ethereal extract was dried ($MgSO_4$), and distilled, giving 2-γ-ethoxy-α-methylbutyrylpyridine, b. p. 146—148°/13 mm. (13 g., 54%), $\lambda_{max.}$ 2270, 2660 Å ($\log_{10}\varepsilon$ 4·21, 3·96) in EtOH. The 2 : 4-*dinitrophenylhydrazone*, prepared in glacial acetic acid, crystallized from aqueous ethanol as yellow prisms, m. p. 141° (Found: C, 56·2, H, 5·2. $C_{18}H_{21}O_5N_5$ requires C, 55·8; H, 5·5%).

1 : 2 : 3 : 4-Tetrahydro-2-methyl-1-oxoquinolizinium Bromide (IX).—A solution of the ketone (VII) (2 g.) in 35% hydrobromic acid (20 ml.) was boiled under reflux for 20 min., then evaporated to dryness under reduced pressure. The residue was dissolved in the minimum quantity of water and treated dropwise with aqueous sodium carbonate, and the liberated bromo-amine was extracted by chloroform. The chloroform extract was dried ($MgSO_4$) and boiled under reflux till an oil separated, then the chloroform was evaporated. The residual bromide would not solidify, but gave a 2 : 4-*dinitrophenylhydrazone*, prepared in glacial acetic acid, which crystallized from aqueous ethanol as yellow needles, m. p. 182° (decomp.) (Found: C, 43·6; H, 3·9. $C_{16}H_{16}O_4N_5Br,H_2O$ requires C, 43·6; H, 4·1%).

2-Methylquinolizinium Picrate (XI; X = *Picrate*).—Treatment of the crude bromide (IX) with acetic anhydride for 1 hr. and treatment of the product with aqueous sodium picrate gave *2-methylquinolizinium picrate*, recrystallized from absolute ethanol as yellow needles, m. p. 162° [65% overall yield from the ketone (VII)] (Found: C, 52·0; H, 3·5. $C_{16}H_{12}O_7N_4$ requires C, 51·6; H, 3·25%), $\lambda_{max.}$ 2270, 2850, 3120, 3200, 3255 Å ($\log_{10}\varepsilon$ 4·54, 3·81, 4·29, 4·29, 4·61) in H_2O. The *perchlorate*, obtained by anionic exchange, crystallised from absolute ethanol as buff needles, m. p. 110·5° (Found: C, 49·1; H, 4·1. $C_{16}H_{16}O_4NCl$ requires C, 49·3; H, 4·1%), $\lambda_{max.}$ 2260, 2855, 3120, 3200, 3260 Å ($\log_{10}\varepsilon$ 4·32, 3·5, 4·1, 4·03, 4·3) in H_2O.

3-Ethoxy-1-phenylpropan-1-ol (VI).—Slow addition of 3-ethoxypropionaldehyde (28 g.) in dry ether (50 ml.) to the stirred Grignard reagent from bromobenzene (50 g.) in dry ether (600 ml.) with subsequent stirring for 1 hr. and working up as for the alcohol (V) gave *3-ethoxy-1-phenylpropan-1-ol*, b. p. 147°/15 mm. (39·5 g., 79·5%), n_D^{25} 1·5075 (Found: C, 73·7; H, 9·0. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·95%).

1-Bromo-3-ethoxy-1-phenylpropane.—Treatment of the alcohol (VI) (30 g.) with phosphorus tribromide (20 g.) as described above gave the bromopropane, b. p. 81—83°/0·15 mm. (23 g., 57%).

2-γ-Ethoxy-α-phenylbutyrylpyridine (VIII).—2-Cyanopyridine (10 g.), stirred in dry ether (100 ml.), was treated with the Grignard reagent from 1-bromo-3-ethoxy-1-phenylpropane (23 g.) in dry ether (250 ml.), and the mixture kept overnight at room temperature. Working up as described above gave, after distillation, 2-cyanopyridine (3 g.) and *2-γ-ethoxy-α-phenylbutyrylpyridine*, b. p. 152°/0·5 mm. (11·5 g., 63·5% on 2-cyanopyridine used) (Found: C, 75·6; H, 7·15. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1%).

1 : 2 : 3 : 4-Tetrahydro-1-oxo-2-phenylquinolizinium Bromide (X).—A solution of the ketone (VIII) (1·38 g.) in 35% hydrobromic acid (20 ml.) was boiled under reflux for 30 min. Cyclization in chloroform as described above gave the bromide as pale green prisms, m. p. 196° (1·06 g., 72%), $\lambda_{max.}$ 2460, 2860, 3770 Å ($\log_{10}\varepsilon$ 3·95, 3·86, 3·92) in EtOH. The *picrate* crystallized from aqueous ethanol as yellow needles, m. p. 152° (Found: C, 56·0; H, 3·3. $C_{21}H_{16}O_8N_4$ requires C, 55·8; H, 3·6%).

2-Phenylquinolizinium Picrate (XII; X = *Picrate*).—Acetic anhydride treatment of the bromide (X) for 30 min. gave 2-phenylquinolizinium picrate (88·4%) which crystallized from absolute ethanol as yellow needles, m. p. 168° (lit.,[6] m. p. 168—170°) (Found: C, 57·8; H, 3·4.

XUM

Calc. for $C_{21}H_{14}O_7N_4$: C, 58·05; H, 3·25%), $\lambda_{max.}$ 2500, 3420 Å ($\log_{10}\varepsilon$ 4·36, 4·54) in H_2O. The perchlorate crystallized from absolute ethanol as colourless needles, m. p. 168° (lit.,[6] m. p. 168—169·5°) (Found: C, 58·6; H, 4·3. Calc. for $C_{15}H_{13}O_4NCl$: C, 58·95; H, 4·0%), $\lambda_{max.}$ 2630, 3420 ($\log_{10}\varepsilon$ 4·18, 4·37) in H_2O.

Methyl β-Methoxyisobutyrate (XIII).—Methyl methacrylate (100 g., freshly distilled from 1 g. of quinol) was added to a solution of sodium (1 g.) in dry methanol (400 ml.), and the mixture boiled under reflux for 30 min. The methanol was removed by distillation and ether (200 ml.) was added to the residue. The ethereal solution was shaken with cold dilute hydrochloric acid, then with aqueous sodium hydroxide, and finally with water. After drying ($MgSO_4$) the ethereal solution was distilled, giving the methyl ester, b. p. 147°/746 mm. (39 g., 30%). Prolonged boiling of the reaction mixture led to a considerable decrease in the yield.

3-Methoxy-2-methylpropan-1-ol (XIV).—To a stirred solution of lithium aluminium hydride (10 g.) in ether (300 ml.) was added the ester (XIII) (39 gm.) in ether (350 ml.); the mixture was boiled for 1 hr., then set aside overnight. Excess of lithium aluminium hydride was decomposed with ethyl acetate, and the mixture treated with water. The ethereal solution was separated, dried ($MgSO_4$), and distilled, giving the alcohol, b. p. 154—155°/733 mm. (25 g., 95%) (lit.,[12] b. p. 154—155°).

1-Chloro-3-methoxy-2-methylpropane (XVI).—This was prepared from the alcohol (XIV) as described by Elderfield, Pitt, and Wempen.[12]

2-γ-Methoxy-β-methylbutyrylpyridine (XVII).—A stirred solution of 2-cyanopyridine (20 g.) in dry ether (150 ml.) was treated with the Grignard reagent from the chloropropane (XVI) (27·5 g.) in ether (300 ml.), and kept overnight at room temperature. Working up as described for the compound (VII) gave the *pyridyl ketone*, b. p. 140—142°/13 mm. (33 g., 64·6%) (Found: C, 68·4; H, 7·95. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8%). The 2 : 4-*dinitrophenylhydrazone*, prepared in glacial acetic acid, crystallized from ethanol as yellow needles, m. p. 125° (Found: C, 54·6; H, 4·85. $C_{17}H_{19}O_8N_5$ requires C, 54·7; H, 5·1%).

1 : 2 : 3 : 4-*Tetrahydro-3-methyl-1-oxoquinolizinium Bromide* (XVIII).—2-γ-Methoxy-β-methylbutyrylpyridine (2 g.) was cyclized as described above. The *bromide* separated from the hot chloroform solution as a solid which recrystallized from ethyl acetate–ethanol as colourless prisms, m. p. 205° (decomp.) (1·8 g., 73·5%) (Found: C, 46·1; H, 5·1. $C_{10}H_{12}ONBr,H_2O$ requires C, 46·2; H, 5·4%), $\lambda_{max.}$ 2750 Å ($\log_{10}\varepsilon$ 3·93) in EtOH. The *picrate* crystallized from absolute ethanol as yellow needles, m. p. 157° (Found: C, 49·2; H, 3·8. $C_{16}H_{14}O_8N_4$ requires C, 49·2; H, 3·6%), $\lambda_{max.}$ 2750 Å ($\log_{10}\varepsilon$ 3·98) in EtOH.

3-Methylquinolizinium Bromide (XIX).—Acetic anhydride treatment of the bromide (XVIII) for 30 min. gave a quantitative yield of *3-methylquinolizinium bromide*, which crystallized from ethyl acetate–ethanol as colourless prisms, m. p. 189° (Found: C, 49·7; H, 5·3. $C_{10}H_{10}NBr,H_2O$ requires C, 49·6; H, 5·0%), $\lambda_{max.}$ 2300, 2860, 3140, 3200, 3280 Å ($\log_{10}\varepsilon$ 4·28, 3·41, 4·03, 3·96, 4·25) in H_2O. The *picrate* crystallized from absolute ethanol as yellow needles, m. p. 182° (Found: C, 51·45; H, 3·3. $C_{16}H_{12}O_7N_4$ requires C, 51·6; H, 3·25%), $\lambda_{max.}$ 2300, 3140, 3210, 3280 Å ($\log_{10}\varepsilon$ 4·53, 4·26, 4·26, 4·48) in H_2O.

3-Ethoxybutan-1-ol (XXI).—Ethyl β-ethoxybutyrate [14] (25 g.) in ether (50 ml.) was added slowly to lithium aluminium hydride (6 g.) in ether (250 ml.), and the mixture kept overnight. Excess of lithium aluminium hydride was decomposed with ethyl acetate, the mixture hydrolyzed, and the ether layer separated, and dried ($MgSO_4$). Distillation gave the butanol, b. p. 163—166°/748 mm. (17 g., 92%), n_D^{25} 1·4155.

1-Bromo-3-ethoxybutane.—Phosphorus tribromide (30 g.) was added slowly to 3-ethoxybutan-1-ol (35·5 g.), the temperature being kept below 60° for 1 hr. The cooled mixture was poured on ice, and the separated organic layer shaken with aqueous sodium hydrogen carbonate, followed by water. The dried ($MgSO_4$) liquid was distilled, giving the bromide, b. p. 159°/747 mm. (41 g., 75%), n_D^{25} 1·4450.

2-γ-Ethoxyvalerylpyridine (XXII).—A stirred solution of 2-cyanopyridine (16 g.) in ether (150 ml.) was treated with the Grignard reagent from 1-bromo-3-ethoxybutane (30 g.), in ether (350 ml.). The yellow complex formed was kept overnight at room temperature. Working up as described above gave the valerylpyridine, b. p. 156—158°/16 mm. (19 g., 55%). The 2 : 4-*dinitrophenylhydrazone* crystallized from 95% ethanol as yellow prisms, m. p. 137° (Found: C, 55·5; H, 5·3. $C_{18}H_{21}O_8N_5$ requires C, 55·8; H, 5·5%).

1 : 2 : 3 : 4-*Tetrahydro-4-methyl-1-oxoquinolizinium Bromide* (XXIII).—A solution of the valerylpyridine (XXII) (2 g.) in 35% hydrobromic acid was boiled under reflux for 10 min.

XUM

(longer boiling led to side reactions and tars were obtained). Worked up as before, the bromide (1·1 g., 47%) had m. p. 170—171° (from ethanol–ether), $\lambda_{max.}$ 2750 Å ($\log_{10}$ ε 3·75) in EtOH. The *picrate* crystallised from absolute ethanol as yellow buffers, m. p. 146° (Found: C, 48·9; H, 3·9. $C_{16}H_{14}O_8N_4$ requires C, 49·2; H, 3·6%).

4-Methylquinolizinium Picrate (XXIV; X = *Picrate*).—Acetic anhydride treatment of the bromide (XXIII) for 30 min. gave 4-methylquinolizinium picrate (65%), m. p. 135° (lit.,[3] m. p. 135—135·5°), $\lambda_{max.}$ 2310, 2910, 3170, 3300, 3560 Å ($\log_{10}$ ε 4·53, 3·83, 4·27, 4·45, 4·26) [lit.,[3] $\lambda_{max.}$ 2300, 2900, 3170, 3300, 3330 Å ($\log_{10}$ ε 4·49, 3·77, 4·23, 4·4, 4·18)] in H_2O.

2-γ-Ethoxybutyrylquinoline (XXV).—1-Benzoyl-2-cyano-1 : 2-dihydroquinoline [17] was converted into 2-cyanoquinoline [18] in 30% yield. The cyanoquinoline (21 g.) stirred in ether (200 ml.) was treated slowly with the Grignard reagent from the 3-ethoxypropyl bromide (30 g.) in ether (350 ml.), and the mixture kept overnight at room temperature. Worked up as described above, the butyrylquinoline was obtained as an oil, b. p. 144—146°/0·05 mm. (28·5 g., 86%). The 2 : 4-*dinitrophenylhydrazone*, prepared in glacial acetic acid, crystallized from 95% ethanol as orange yellow prisms, m. p. 137° (Found: C, 59·6; H, 4·85. $C_{21}H_{21}O_5N_5$ requires C, 59·6; H, 5·0%).

1 : 2 : 3 : 4-*Tetrahydro-4-oxobenzo*[c]*quinolizinium Bromide* (XXVIII).—A solution of 2-γ-ethoxybutyrylquinoline (2 g.) in 35% hydrobromic acid (20 ml.) was boiled under reflux for 20 min., then concentrated under reduced pressure to 5 ml. The solution was cooled and diluted, and the precipitated bromo-amine was extracted with chloroform. The chloroform extract was dried ($MgSO_4$) and boiled under reflux. Concentration of the chloroform solution gave the crystalline bromide, m. p. 188—189° (1·72 g., 75%). The picrate crystallized from absolute alcohol containing a trace of picric acid as yellow prisms, m. p. 151°. The *phenylhydrazone iodide* was obtained by heating together the bromide and phenylhydrazine in glacial acetic acid, diluting the mixture, and precipitating the insoluble iodide by addition of aqueous sodium iodide; it crystallized from absolute ethanol as red needles, m. p. 264° (Found: C, 54·6; H, 4·5. $C_{19}H_{18}N_3I$ requires C, 54·95; H, 4·4%).

Benzo[c]*quinolizinium Picrate* (XXXI).—Acetic anhydride treatment of the bromide (XXVIII) for 30 min. gave *benzo*[c]*quinolizinium picrate* (63%) which crystallized from absolute ethanol as yellow needles, m. p. 188—189° (Found: C, 56·0; H, 3·3. $C_{19}H_{12}O_7N_4$ requires C, 55·9; H, 3·0%), $\lambda_{max.}$ 2270, 2500, 3050, 3480, 3640 Å ($\log_{10}$ ε 4·48, 4·59, 3·93, 4·41, 4·46) in H_2O. The *perchlorate* crystallized from absolute ethanol as buff needles, m. p. 188—189° (Found: C, 55·4; H, 3·45. $C_{13}H_{10}O_4NCl$ requires C, 55·8; H, 3·6%), $\lambda_{max.}$ 2270, 2525, 3000, 3470, 3640 Å ($\log_{10}$ ε 4·27, 4·48, 3·67, 4·11, 4·2) in H_2O.

1-*γ-Ethoxybutyryliso*quinoline (XXVI).—2-Benzoyl-1-cyano-1 : 2-dihydro*iso*quinoline [19] was converted into 1-cyano*iso*quinoline as described by Hoste and Gillis.[20] A stirred solution of 1-cyano*iso*quinoline (11 g.) in ether (120 ml.) was treated with the Grignard reagent from 3-ethoxypropyl bromide (15 gm.) in ether (200 ml.) and kept overnight at room temperature. Working up as described above gave the butyryl*iso*quinoline, b. p. 137—139°/0·1 mm. (10·5 g., 60·5%). The 2 : 4-*dinitrophenylhydrazone* crystallized from 95% ethanol as yellow prisms, m. p. 139° (Found: C, 60·0; H, 5·0. $C_{21}H_{21}O_5N_5$ requires C, 59·6; H, 5·0%).

1 : 2 : 3 : 4-*Tetrahydro-1-oxobenzo*[a]*quinolizinium Bromide* (XXIX).—A solution of 1-γ-ethoxybutyryl*iso*quinoline (2 g.) in 35% hydrobromic acid (20 ml.) was boiled under reflux for 20 min., then concentrated to 5 ml. Dilution precipitated the bromo-amine which was extracted with chloroform, dried ($MgSO_4$), and boiled under reflux. The solid bromide separated as yellow prisms, m. p. 210° (decomp.) (1·9 g., 79·6%). The *picrate* crystallized from water as yellow prisms, m. p. 146° (Found: C, 53·8; H, 3·3. $C_{19}H_{14}O_8N_4$ requires C, 3·5; H, 3·3%). The *phenylhydrazone iodide*, prepared as described above, crystallized from absolute alcohol as orange-red prisms, m. p. 258—259° (Found: C, 55·0; H, 4·6. $C_{19}H_{18}N_3I$ requires C, 54·95; H, 4·4%).

Benzo[a]*quinolizinium Picrate* (XXXII; X = *Picrate*).—Acetic anhydride treatment of the bromide (XXIX) for 20 min. gave *benzo*[a]*quinolizinium picrate* (66·4%), yellow needles (from absolute ethanol), m. p. 178° (Found: C, 56·0; H, 3·3. $C_{19}H_{12}O_7N_4$ requires C, 55·9;

[17] Reissert, *Ber.*, 1905, **38**, 610.
[18] Kaufmann and Dändliker, *Ber.*, 1913, **46**, 2924.
[19] Reissert, *Ber.*, 1905, **38**, 3415.
[20] Hoste and Gillis, *Mededel. Koninkl. Vlaam. Acad. Wetenschap. Belg. Klasse Wetenschap.*, 1951, **13**, 3; *Chem. Abs.*, 1952, **46**, 5474.

XUM

H, 3·0%), $\lambda_{max.}$ 2400, 2650, 3370, 3530 Å ($\log_{10}\varepsilon$ 4·56, 4·41, 4·39, 4·49) in H_2O. The *perchlorate* crystallized from absolute ethanol as colourless needles, m. p. 197° (Found: C, 55·4; H, 3·3. $C_{13}H_{10}O_4NCl$ requires C, 55·8; H, 3·6%), $\lambda_{max.}$ 2360, 2770, 3230, 3370, 3530 Å ($\log_{10}\varepsilon$ 4·38, 4·32, 3·75, 4·04, 4·17) in H_2O.

Benzo[b]*quinolizinium Picrate* (XXXIII; X = *Picrate*).—A solution of 1 : 2 : 3 : 4-tetrahydro-1-oxobenzo[*b*]quinolizinium bromide [8] (0·133 g.) in acetic anhydride (20 ml.) containing a drop of concentrated sulphuric acid was boiled under reflux for 3 hr. The solution was cooled, an equal volume of water added, and the bulk of the solvent removed under reduced pressure. The remaining solution was treated with aqueous sodium picrate, giving benzo[*b*]quinolizinium picrate, which crystallized from 95% ethanol as yellow prisms, m. p. 215° (decomp.) (0·073 g., 62%) (lit.,[15] m. p. 214—216°).

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Department of Chemistry,
The University College of North Staffordshire,
Keele, Staffordshire.

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615. *Deoxynucleosides and Related Compounds. Part VI.* The Synthesis of 2-Thiouridine and of 3′-Deoxyuridine.*

By D. M. Brown, D. B. Parihar, Sir Alexander Todd, and S. Varadarajan.

2′ : 3′-*O*-*iso*Propylidene-O^2 : 5′-*cyclo*uridine and 2′ : 3′-*O*-*iso*propylidene-5′-*O*-toluene-*p*-sulphonyluridine both react with sodium ethyl sulphide to give 5′-deoxy-5′-ethylthio-2′ : 3′-*O*-*iso*propylideneuridine. The same reaction applied to O^2 : 2′-*cyclo*uridine affords 3′-deoxy-3′-ethylthiouridine from which 3′-deoxyuridine is obtained by treatment with Raney nickel. 2′ : 3′-*O*-*iso*Propylidene-O^2 : 5′-*cyclo*uridine with hydrogen sulphide and triethylamine gives 2′ : 3′-*O*-*iso*propylidene-2-thiouridine from which 2-thiouridine can be obtained. The thiolation reaction also affords polysulphides of the probable structure R-S_{2n}-R where $n = 1$, 2, or 3, and R is an *iso*propylidene-2-deoxy-2-uridinyl residue.

The structures of the naturally occurring deoxyribonucleosides have been completely elucidated;[1] they are all β-2′-deoxy-D-ribofuranosides. Several unsuccessful attempts have been made in the past to effect their synthesis. Thus, following the work of Levene and Cortese,[2] Davoll and Lythgoe [3] condensed silver theophylline with, *inter alia*, 3 : 4-di-*O*-acetyl-2-deoxyribosyl chloride and obtained both α- and β-2′-deoxyribopyranosyltheophylline. The lability of halides derived from furanose sugars would almost certainly complicate any extension of this method to deoxyribofuranose derivatives. In addition, recent views [4] on the mechanism of such condensations suggest that the formation of the β-anomer in ribonucleoside syntheses depends on participation by the neighbouring 2-*O*-acyl group; in deoxynucleoside syntheses this control is lacking, as was indeed shown by Davoll and Lythgoe [3] when they isolated both anomeric forms. As another approach, methods involving ring-opening of 2′ : 3′-anhydropentofuranosides were studied [5] but it was found

* Part V, *J.*, 1955, 816.

[1] Lythgoe, *Ann. Reports*, 1944, **41**, 200; Brown and Lythgoe, *J.*, 1950, 1990; Andersen, Hayes, Michelson, and Todd, *J.*, 1954, 1882; Michelson and Todd, *J.*, 1955, 816.
[2] Levene and Cortese, *J. Biol. Chem.*, 1931, **92**, 53.
[3] Davoll and Lythgoe, *J.*, 1949, 2526.
[4] Ness, Fletcher, and Hudson, *J. Amer. Chem. Soc.*, 1951, **73**, 296; Baker, in the Ciba Foundation Symposium on "The Chemistry and Biology of Purines," J. and A. Churchill, London, 1957, p. 120.
[5] Davoll, Lythgoe, and Trippett, *J.*, 1951, 2230.

that, in agreement with the experience of others,[6,7] attack was predominantly at the 3′-position and that only traces of the desired 2′-deoxy-compounds were formed.

Since 5-protected 2-deoxy-D-ribose derivatives are now available [8] it is probable that a deoxynucleoside synthesis based on, for example, the type used successfully for adenosine [9] could be elaborated. But it seemed that syntheses from the available ribonucleosides would be more attractive in that the required lactol ring-size and glycosidic configuration would be already established in the starting material. We describe here experiments on these lines which, however, led to 3′-deoxyuridine, and in the succeeding paper [10] a route is developed for the synthesis of 2′-deoxyuridine and of thymidine.

Our earlier studies of the *cyclo*nucleosides (II and VII) derived from uridine showed that in reactions involving ring-opening, nucleophilic attack occurred at $C_{(2)}$ of the pyrimidine ring. Thus, O^2 : 2′-*cyclo*uridine (VII) was converted into the arabinoside, spongouridine, by acid.[11] The O^2 : 5′-*cyclo*uridine derivative (II) gave uridine with acid, and with methanolic ammonia gave O^2-methyl-2′ : 3′-*iso*propylideneuridine, which by longer treatment with the same reagent yielded *iso*propylidene*iso*cytidine.[12] We have now found that O^2 : 2′-*cyclo*uridine (VII) also reacts with methanolic ammonia to give 3-β-D-arabofuranosyl*iso*cytosine (VI), the structure of which follows from its elementary analysis and the identity of its ultraviolet spectral characteristics with those of *iso*propylidene-*iso*cytidine.*

It was of interest to find if nucleophilic displacement on the *cyclo*nucleosides could be effected with alkyl–oxygen fission, *i.e.*, on a sugar ring-carbon atom, since this might give a method for deoxynucleoside synthesis. The *cyclo*uridine (II) reacted readily with hydrogen sulphide and triethylamine [13] in dimethylformamide but the major product was 2′ : 3′-*O*-*iso*propylidene-2-thiouridine (I). The constitution of this product followed from its composition and the close similarity of its ultraviolet absorption spectrum to that of 3-methyl-2-thiouracil.[14] On hydrolysis with dilute acetic acid 2-thiouridine was obtained.† It is probably identical with the thiouracil riboside formed enzymically from thiouracil and ribofuranose 1-phosphate.[16] Syntheses of 2-thiouridine [17] and the related 3-glucopyranosyl-2-thiouracil [18] by other routes have also been described. In the reaction of the *cyclo*uridine (II) with hydrogen sulphide, three other products, A, B, and C, were also obtained, A being formed when the least amount of triethylamine was used and C when a large excess of base was present. Their empirical formulæ indicated that they were polysulphides. Their ultraviolet spectra were different from those of uridine and 2-thiouridine. They had almost identical infrared spectra. Thus derivatives of 5′-thiouridine were excluded on spectral grounds. We formulate A, B, and C tentatively as di-, tetra-, and hexa-sulphides with the general structure (IV; $n = 1, 2, 3$). This would account

* We thank Dr. D. Shugar, Academy of Sciences, Warsaw, for drawing our attention to the presence of an impurity in a sample of O^2 : 2′-*cyclo*uridine which we had provided. This impurity has been identified as compound (VI) and is formed during the preparation of the *cyclo*uridine from 5′-*O*-acetyl-2′-*O*-toluene-*p*-sulphonyluridine by the action of methanolic ammonia (see p. 3032).

† A preliminary announcement of this result and some other observations on *cyclo*nucleoside chemistry have already been made.[15]

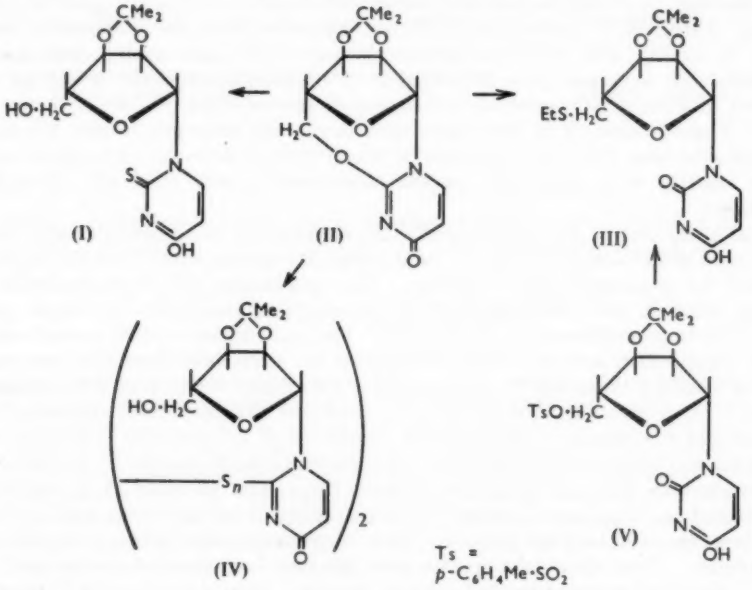
[6] Mukherjee and Todd, *J.*, 1947, 969.
[7] Allerton and Overend, *J.*, 1951, 1480.
[8] Kenner and Richards, *J.*, 1954, 3277.
[9] Kenner, Taylor, and Todd, *J.*, 1949, 1621.
[10] Brown, Parihar, Reese, and Todd, following paper.
[11] Brown, Todd, and Varadarajan, *J.*, 1956, 2388.
[12] *Idem*, *J.*, 1957, 868.
[13] Fairfull, Lowe, and Peak, *J.*, 1952, 742.
[14] Shugar and Fox, *Bull. Soc. chim. belges*, 1952, **61**, 293.
[15] Brown, Todd, and Varadarajan in the Ciba Foundation Symposium on "The Chemistry and Biology of Purines," J. and A. Churchill, Ltd., London, 1957, p. 108.
[16] Stromінger and Friedkin, *J. Biol. Chem.*, 1954, **208**, 663; see also Jeener and Roseeles, *Biochim. Biophys. Acta*, 1953, **11**, 438; Jeener, *ibid.*, 1954, **13**, 148; Matthews, *ibid.*, 1956, **19**, 559.
[17] Shaw and Warrener, *Proc. Chem. Soc.*, 1957, 351.
[18] Fox, Chang, and Davoll, *Fed. Proc.*, 1954, **13**, 211.

XUM

for their insolubility in alkali and the fact that B and C, when heated to 180°, liberate sulphur and are converted into A.

When the action of the more powerful nucleophilic reagent sodium ethyl sulphide was studied it was found that O^2 : 5′-*cyclo*uridine (II) was converted smoothly into 5′-deoxy-5′-ethylthio-2′ : 3′-*O*-*iso*propylideneuridine (III). This compound had a uridine-like ultraviolet spectrum and, moreover, was formed directly with the same reagent from 2′ : 3′-*O*-*iso*propylidene-5′-*O*-toluene-*p*-sulphonyluridine (V).[19] Thus ring-opening in the *cyclo*nucleoside could be effected in either direction depending on the reagent and conditions employed.

With this knowledge we decided to study the action of sodium ethyl sulphide on

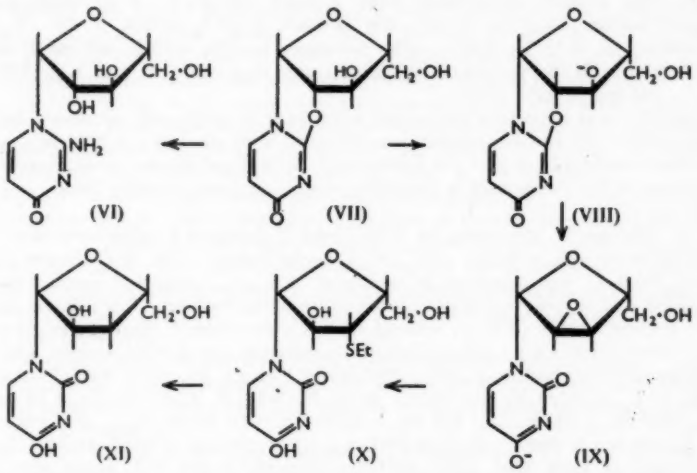


O^2 : 2′-*cyclo*uridine (VII) as a possible route to 2′-deoxyuridine. Reaction was slow in dimethylformamide but at 100° with a large excess of reagent a product was obtained in good yield. From its composition it was clearly a deoxyethylthiouridine and since its ultraviolet spectrum was very similar to that of uridine substitution had occurred on the sugar residue. Surprisingly, too, it gave a reaction, on paper chromatograms, with the cysteine–sulphuric acid reagent,[20] hitherto considered[21,22] specific for 2-deoxy-sugars and their glycosides.

The material was acetylated, and heated in aqueous ethanol with Raney nickel. Reaction was slow and even after 30 hours starting material appeared to be present, but a product very similar to 2′-deoxyuridine had been formed. Reduction of the pyrimidine ring also seemed to occur in part and model experiments showed that conversion of 3-methyluracil into 4 : 5-dihydro-3-methyluracil was essentially complete in five hours. A reaction time of two hours was finally chosen and counter-current distribution of the deacetylated mixture separated unchanged starting material from the product which was formed in small yield. It was a deoxynucleoside which could not be distinguished from

[19] Levene and Tipson, *J. Biol. Chem.*, 1934, **106**, 113.
[20] Buchanan, *Nature*, 1951, **168**, 1091
[21] Stumpf, *J. Biol. Chem.*, 1947, **169**, 367.
[22] Dische, *Proc. Soc. Exp. Biol. Med.*, 1944, **55**, 217.

natural 2′-deoxyuridine [23] on paper chromatograms and, like it, gave a positive cysteine–sulphuric acid reaction. But the crystalline material had a higher melting point than 2′-deoxyuridine and the infrared spectra of the two compounds, although very similar, were distinguishable. The synthetic substance was degraded by reduction followed by hydrolysis [24] and the sugar produced compared with all the 2- and 3-deoxypentoses. Paper electrophoresis in borate buffer [25] and paper chromatography established its identity as 3-deoxyribose. Thus the original product is 3′-deoxyuridine (XI), so the ethylthio-compound must have been 3′-deoxy-3′-ethylthiouridine. A probable explanation for the production of the latter from O^2 : 2′-*cyclo*uridine is that the primary action of sodium



ethyl sulphide is to remove a proton from the 3′-hydroxyl group. The anion (VIII) then undergoes conversion into the 2′ : 3′-anhydrouridine anion (IX) and indeed these may be in mobile equilibrium. The latter is then attacked by the reagent, to give the 3′-deoxy-3′-ethylthio-compound, which must on this basis have the *xylo*-configuration (X). It is well known that the epoxy-ring in 2 : 3-anhydropentosides is opened predominantly by attack at the 3-position, only 1—2% of reaction at the 2-position being observed. The crude deoxynucleoside recovered from mother-liquors, when degraded to the sugar, gave, in addition to 3-deoxyribose, a small amount of 2-deoxyribose, further evidence of the formation of a 2 : 3-anhydro-intermediate.

When 5′-*O*-acetyluridine is toluene-*p*-sulphonylated, substitution occurs mainly in the 2′-position.[11] Some 3′-*O*-toluene-*p*-sulphonyluridine is also produced, however, and has now been isolated from the mother-liquors from the 2′-compound by treatment with methanolic ammonia. The 3′-isomer, the structure of which was established by degradation, is unaffected by the latter reagent, in contrast to the rapid formation of O^2 : 2′-*cyclo*uridine from the 2′-*O*-toluene-*p*-sulphonyl derivative.

Experimental

Evaporations were done under reduced pressure. Paper chromatography was carried out with Whatman No. 1 paper and the solvent systems (A) butan-1-ol saturated with water, (B) butan-1-ol–acetic acid–water (5 : 2 : 3), and (C) propan-2-ol–aqueous 1% $(NH_4)_2SO_4$ (2 : 1). Counter-current distributions were effected in an automatically operated apparatus (20·5 c.c. phase) with the ethyl acetate–water system.

[23] Dekker and Todd, *Nature*, 1950, **166**, 157.
[24] Burke, *J. Org. Chem.*, 1955, **20**, 643.
[25] Foster, *Chem. and Ind.*, 1952, 828.

XUM

3′-O-*Toluene*-p-*sulphonyluridine*.—To a solution of 5′-*O*-acetyluridine (13 g.) in dry pyridine (70 c.c.) was added toluene-*p*-sulphonyl chloride (9·51 g.), and the solution set aside overnight. Ethanol (100 c.c.) was added and solvents were removed. Water (200 c.c.) was added to the red syrup and after 10 hr. the solid was collected, triturated with ethanol, and crystallised from methanol, giving needles (9·8 g.) of 5′-*O*-acetyl-2′-*O*-toluene-*p*-sulphonyluridine, m. p. 176—177° as described earlier.[11] The aqueous filtrate and alcoholic washings were combined and evaporated. The residual syrup was treated with half-saturated methanolic ammonia (300 c.c.) and left overnight, then methanol and ammonia were removed and the residue submitted to counter-current distribution (47 transfers). *O*^{2} : 2′-*cyclo*Uridine was present in tubes 1–4 and the product in tubes 32—45. The contents of the latter tubes were pooled and evaporated. The residue crystallised from ethanol (20 c.c.). 3′-O-*Toluene*-p-*sulphonyluridine* formed needles (3·4 g.), m. p. 205—206° (Found: C, 48·1; H, 4·3; N, 6·9. $C_{16}H_{18}O_8N_2S$ requires C, 48·2; H, 4·5; N, 7·0%). The substance had R_F 0·79 in solvent B and gave a negative reaction with the periodate–benzidine spray reagent.[26] It had $\lambda_{max.}$ 261—262 and 225 mμ, $\lambda_{min.}$ 241 mμ in 95% EtOH.

The compound was recovered unchanged when kept in methanolic ammonia for 7 days at room temperature. No isolable product was obtained with ammonia at 100° in a sealed tube, or with sodium methoxide (1 mol.) in methanol. No sodium toluene-*p*-sulphonate separated when a solution of the compound in acetonylacetone containing sodium iodide was heated at 100° for 24 hr.

Action of Methanolic Ammonia on 5′-O-*Acetyl*-2′-O-*toluene*-p-*sulphonyluridine*: *Isolation of* 3-β-D-*Arabofuranosyl*isocytosine *and* O^2 : 2′-cyclo*Uridine*.—The 2′-*O*-toluene-*p*-sulphonyl derivative [11] (10·0 g.) was dissolved in methanol (400 c.c.), saturated methanolic ammonia (400 c.c.) added, and the solution kept at room temperature for 7 hr. The solvent was removed and the crystalline residue (5·22 g.) washed with a little ethanol, then recrystallised, slowly, from 80% ethanol (40 c.c.). 3-β-D-*Arabofuranosyl*isocytosine formed prisms which on one further recrystallisation had m. p. 235—236° (yield 1·91 g.), R_F (in C) 0·60 (Found: C, 45·1; H, 5·6; N, 17·1. $C_9H_{13}O_5N_3$ requires C, 44·4; H, 5·3; N, 17·3%). Light absorption: in water, $\lambda_{max.}$ 257 mμ (ε 6370), $\lambda_{min.}$ 237 mμ (ε 5950); in 0·1N-NaOH, $\lambda_{max.}$ 260, 228 mμ (ε 6150, 11,130), $\lambda_{min.}$ 250 mμ (ε 5800); in 0·1N-HCl, $\lambda_{max.}$ 258, 219 mμ (ε 8500, 10,340), $\lambda_{min.}$ 239 mμ (ε 5390). Bands at 3330, 3260, 1589 cm.$^{-1}$ due probably to the NH_2 group were present in the infrared spectrum. The substance gave a negative reaction with the periodate reagent [27] on paper chromatograms.

To the mother-liquors, after isolation of the *iso*cytosine derivative, water was added to give a 50% aqueous ethanol solution, which was kept at 0° for several days. *O*^{2} : 2′-*cyclo*-Uridine separated slowly and formed stout rods (2·7 g.), m. p. 234—236°, from 95% ethanol. It had R_F 0·68 in solvent C, and was identical in all respects with an authentic specimen.[11] Paper chromatography showed that after treatment for 5 days with methanolic ammonia it was converted into the above *iso*cytosine derivative.

5′-*Deoxy*-5′-*ethylthio*-2′ : 3′-iso*propylideneuridine*.—(*a*) Anhydrous sodium ethyl sulphide (200 mg.) was added to a solution of 2′ : 3′-*O*-*iso*propylidene-O^2 : 5′-*cyclo*uridine [12] (100 mg.) in anhydrous dimethylformamide (30 c.c.); after 15 hr. at room temperature water and dilute acetic acid were added and the solution was extracted with chloroform. The extract was evaporated and the residue crystallised from ethanol, giving the *product* (65 mg.) as colourless rods, m. p. 140° (Found: C, 51·2; H, 6·2; N, 8·4. $C_{14}H_{20}O_5N_2S$ requires C, 51·2; H, 6·1; N, 8·5%), $\lambda_{max.}$ 259 mμ (ε 9850), $\lambda_{min.}$ 229 mμ (ε 2460) in 95% EtOH, infrared absorption bands in the carbonyl region were present at 1622, 1687, 1711, and 1773 cm.$^{-1}$.

(*b*) 2′ : 3′-*iso*Propylidene-5′-*O*-toluene-*p*-sulphonyluridine [13] (1·5 g.) was dissolved in dry dimethylformamide (30 c.c.), and sodium ethyl sulphide (3·0 g.) added. The solution was heated at 100° for 2 hr. with exclusion of moisture, then cooled in ice, diluted with ice-water (60 c.c.), and acidified with dilute sulphuric acid. The solution was extracted with chloroform (2 × 100 c.c.), and the extract washed with water (50 c.c.) and evaporated to dryness. The residue was evaporated twice with ethanol *in vacuo* and finally crystallised from hot ethanol. The product (0·41 g.), R_F 0·91 in solvent B (Found: C, 51·2; H, 6·3; N, 8·4%), had m. p. 142° undepressed by the compound prepared by method (*a*); the infrared spectra of the two materials were identical.

[26] Sykes and Todd, "The Chemistry of Penicillin," Oxford Univ. Press, 1949, p. 185.
[27] Buchanan, Dekker, and Long, *J.*, 1950, 3162.

XUM

5′-Deoxy-5′-ethylthiouridine.—The mother-liquors from the crystallisation of the *iso*propylidene derivative in preparation (*b*) above were kept for some time in the cold. *5′-Deoxy-5′-ethylthiouridine* separated and on recrystallisation from ethanol formed small prisms (0·58 g.), m. p. 177—178°, R_F 0·74 in B (Found: C, 45·8; H, 5·7; N, 9·75. $C_{11}H_{16}O_5N_2S$ requires C, 45·8; H, 5·6; N, 9·7%). It gave a positive periodate reaction [27] on paper chromatograms.

*2′ : 3′-O-iso*Propylidene-2-thiouridine *and Di-(2-deoxy-2′ : 3′-O-iso*propylidene-2-uridinyl) *Disulphide* (IV; $n = 1$).—Dry hydrogen sulphide was passed through a solution of *2′ : 3′-O-iso*propylidene-O^2 : *5′-cyclo*uridine (1·5 g.) in anhydrous dimethylformamide (20 c.c.) containing triethylamine (1 c.c.) for 10 hr. The green solution was set aside overnight, then evaporated to dryness. The residue was dissolved in ethanol (50 c.c.) and on concentration to 25 c.c. deposited crystals (350 mg.). Recrystallisation of these from ethanol afforded the *disulphide* in thin plates, m. p. 205—206° (Found: C, 47·9; H, 5·4; N, 9·0; S, 10·7. $C_{24}H_{30}O_{10}N_4S_2$ requires C, 48·2; H, 5·1; N, 9·4; S, 10·7%), $\lambda_{infl.}$ 210—212 mμ (ε 12,700) in 95% EtOH. Infrared absorption bands in the carbonyl region were at 1675, 1714, 1735 cm.$^{-1}$.

The mother-liquors on evaporation gave a yellow oil which, after several days, deposited crystals (710 mg.). These were washed with cold ethanol and recrystallised, affording *2′ : 3′-O-iso*propylidene-2-thiouridine in prisms, m. p. 192°, R_F 0·85 in A (Found: C, 48·5; H, 5·2; N, 9·3; S, 10·6. $C_{12}H_{16}O_5N_2S$ requires C, 48·0; H, 5·4; N, 9·3; S, 10·7%).

*Di-(2-deoxy-2′ : 3′-O-iso*propylidene-2-uridinyl) *Tetrasulphide* (V; $n = 2$).—*iso*Propylidene-O^2 : *5′-cyclo*uridine (0·5 g.) was dissolved in a mixture of dimethylformamide (6 c.c.) and triethylamine (1 c.c.). Passing in hydrogen sulphide changed the colour of the solution to green, blue, orange, and finally red. The solution was worked up as above and yielded the *tetrasulphide* (90 mg.) which formed colourless plates or needles, shrinking at 180° and melting at 232° (decomp.) (Found: C, 43·3; H, 4·7; N, 8·1; S, 20·3. $C_{24}H_{30}O_{10}N_4S_4$ requires C, 43·5; H, 4·6; N, 8·5; S, 19·4%).

The mother-liquors on concentration yielded *iso*propylidene-2-thiouridine.

The tetrasulphide was converted into the above disulphide with loss of sulphur when it was heated in an open tube at 180—185° in a paraffin bath. Identity was established by m. p., mixed m. p., and analysis.

*Di-(2-deoxy-2′ : 3′-O-iso*propylidene-2-uridinyl) *Hexasulphide* (V; $n = 3$).—The reaction was carried out as above but with *cyclo*nucleoside (0·5 g.) in dimethylformamide (6 c.c.) and triethylamine (5 c.c.). The *hexasulphide* crystallised from ethanol in colourless needles (0·23 g.) which became yellow at 175° and decomposed at 215° (Found: C, 39·1; H, 3·9; N, 7·8; S, 26·5. $C_{24}H_{30}O_{10}N_4S_6$ requires C, 39·7; H, 4·2; N, 7·7; S, 26·5%), $\lambda_{max.}$ 262 mμ (ε 2565), $\lambda_{min.}$ 253 mμ (ε 3040) in 95% EtOH.

The mother-liquors from the reaction afforded *2′ : 3′-O-iso*propylidene-2-thiouridine.

The hexasulphide when heated at 180° gave the disulphide and sulphur.

2-Thiouridine.—A solution of *2′ : 3′-O-iso*propylidene-2-thiouridine (0·3 g.) in 40% acetic acid (120 c.c.) was heated under reflux for 2 hr. The residue after removal of solvent was crystallised twice from ethanol, affording the *product* (155 mg.) in thick pale yellow prisms, m. p. 205—207°, with sintering at 195° (Found: C, 41·6; H, 4·9; N, 10·6. $C_9H_{12}O_5N_2S$ requires C, 41·5; H, 4·6; N, 10·8%), $\lambda_{max.}$ 272—273, 218 mμ (ε 11,300, 13,100), $\lambda_{min.}$ 243 mμ (ε 4230) in H_2O, $\lambda_{max.}$ 270, 240 mμ (ε 12,700, 19,300), $\lambda_{min.}$ 260·5 mμ (ε 12,200) in 0·1N-NaOH.

3′-Deoxy-3′-ethylthiouridine.—O^2 : *2′-cyclo*Uridine (5·0 g.) and sodium ethyl sulphide (25 g.) were heated at 100° in anhydrous dimethylformamide (650 c.c.) with stirring for 10 hr.; sodium formate separated during this period. A further 25 g.) of sodium ethyl sulphide was added and heating continued for 12 hr. After cooling, solid carbon dioxide was added in excess, solvent was removed, and the solid residue dissolved in water (200 c.c.). Sodium ions were removed by passage through a column (2·6 × 25 cm.) of Dowex-50 resin (H^+ form), and the column washed with water (5 l.). Eluate and washings were taken to dryness and the pale yellow residue was subjected to counter-current distribution (166 transfers). The contents of tubes 31—72 (which appeared to contain a single substance of R_F 0·66 in solvent A) were pooled and evaporated. The residue did not crystallise, so its ethanolic solution was filtered and taken to dryness, to give the *product* as a colourless glass (3·5 g.) (Found, in material dried at 50°/0·1 mm. for 12 hr. over P_2O_5: C, 45·9; H, 6·0; N, 9·9. $C_{11}H_{16}O_5N_2S$ requires C, 45·8; H, 5·6; N, 9·7%).

It had $\lambda_{max.}$ 260 mμ, $\lambda_{min.}$ 230 mμ. On oxidation with metaperiodate an uptake of 0·71 mole/mole in 18 hr. was observed. Acetylation of the oxidation solution and extraction gave

a crude product whose infrared spectrum showed a band at 1040 cm.$^{-1}$, possibly indicative of a sulphoxide group.[26]

3′-Deoxyuridine.—3′-Deoxy-3′-ethylthiouridine (3·4 g.) was acetylated in pyridine (20 c.c.) with acetic anhydride (35 c.c.) at room temperature overnight and the solution worked up by addition of ethanol and evaporation. The acetylated material (4·5 g.) (single spot on chromatograms, R_F 0·87 in A) was dissolved in 1 : 3 water–ethanol (150 c.c.), six drops of aqueous ammonia and Raney nickel (22 c.c. of sludge) were added, and the mixture was boiled for 2 hr. under reflux. Catalyst was filtered off and washed with warm ethanol (500 c.c.), and filtrate and washings were evaporated, giving a syrup (3·4 g.). This was deacetylated with half-saturated methanolic ammonia (60 c.c.) during 7 hr., and solvent again removed. The product when chromatographed in solvent A showed two spots: starting material of R_F 0·66, and the product of R_F 0·29, both positive to the cysteine spray reagent. The mixture was submitted to counter-current distribution (149 transfers). The starting material (2·1 g.) was recovered from tubes 28—70. The required deoxyuridine was present in tubes 1—14. Except for those of tube 1, which contained some uncharacterised impurities, the contents of the tubes 2—14 were pooled and evaporated. The residue (482 mg.) was dissolved in dry ethanol (4 c.c.). After 24 hr. crystalline uracil (12 mg.) was deposited and removed. The mother-liquor was concentrated (3 c.c.), dry ether (3 c.c.) added, and the product allowed to crystallise. Recrystallised from the same solvent *3′-deoxyuridine* formed needles (88 mg.), R_F 0·29 (in A), m. p. 178° depressed to 155° in admixture with 2′-deoxyuridine (Found: C, 47·8; H, 5·3; N, 12·4. $C_9H_{12}O_5N_2$ requires C, 47·4; H, 5·3; N, 12·3%), $\lambda_{max.}$ 262 mμ (ε 9660), $\lambda_{min.}$ 230 mμ (ε 1710) in 95% EtOH.

The substance had R_F values identical with those of 2′-deoxyuridine in all of the four solvent systems but the pink colour produced with the cysteine–sulphuric acid spray reagent required 1·5 times as long to develop at 85°. Paper electrophoresis did not distinguish the two materials.

The deoxynucleoside (15 mg.) was reduced and hydrolysed by Burke's method,[24] and the deoxy-sugar obtained was compared with all the 2- and 3-deoxypentoses on chromatograms in the butan-1-ol–ethanol–water (4 : 1 : 5) system (40 hr. irrigation) and on electrophoretograms in borate buffer.[25] The results are collected in the Table.

Deoxypentose	R_F	Spray 1	Spray 2	Spray 3	Electrophoretic migration (cm.)
2-Deoxyribose	0·39	Yellow-brown	Pink (5 min.)	Purple (5 min.)	+1·1
2-Deoxyxylose	0·44	,,	,,	,,	−0·4
3-Deoxyribose	0·45	Pink	Pink (10—15 min.)	—	+6·8
Hydrolysis product ...	0·45	,,	,,	—	+6·8
3-Deoxyarabinose	0·41	,,	,,	—	+5·6
D-Glucose	—	Brown	—	—	+9·0

Spray reagents: (1) aniline phthalate (Partridge, *Nature*, 1949, **164**, 443); (2) cysteine–sulphuric acid; [26] (3) diphenylamine.[27]

The impure 3′-deoxyuridine isolated from mother-liquors when reduced and hydrolysed as above contained, in addition to 3-deoxyribose, small amounts of 2-deoxyribose.

3-Deoxyribose.—This was prepared in solution by reduction of methyl 2 : 3-anhydro-α-riboside [6] (40 mg.) with lithium aluminium hydride by the method of Allerton and Overend,[7] followed by acid hydrolysis. Its chromatographic characteristics are recorded in the Table. With the diphenylamine spray reagent a trace of 2-deoxyribose was detected as a contaminant.

3-Deoxyarabinose.—This was prepared as above by lithium aluminium hydride reduction of 2′ : 3′-anhydrolyxofuranosyltheophylline [5] (100 mg.) followed by hydrolysis. The substance was not isolated but was used directly for the chromatographic study.

Isolation of Ribose from 3′-O-Toluene-p-sulphonyluridine.—The toluene-*p*-sulphonyl derivative (400 mg.) was reduced with sodium amalgam, then hydrolysed by the procedure applied earlier [26] to methylated methyl 2-*O*-toluene-*p*-sulphonylribofuranoside. The sugar was obtained as a syrup. Paper chromatography in three solvent systems showed it to be identical with D-ribose and distinguishable from lyxose, xylose, and arabinose. The syrup in methanol (10 c.c.) was treated with toluene-*p*-sulphonylhydrazine (200 mg.), boiled for 0·5 hr., then set aside in the cold for some days. Ribose toluene-*p*-sulphonylhydrazone separated in plates

[26] Brown, Fasman, Magrath, and Todd, *J.*, 1954, 1448.

and on recrystallisation from 95% ethanol had m. p. 159—160° undepressed by an authentic specimen.[29] The infrared spectra of the samples were identical.

Thanks are extended to Dr. Gladys Woodward, Biochemical Research Foundation, Newark, Del., for a sample of 2-deoxyxylose and to Dr. T. J. Bardos, Armour & Co., Chigaco, for 2'-deoxyuridine. We are grateful to the Ministry of Education, Government of India, for an Overseas Scholarship (to D. B. P.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, April 8th*, 1958.]

[29] Easterby, Hough, and Jones, *J.*, 1951, 3416.

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616. *Deoxynucleosides and Related Compounds. Part VII.* The Synthesis of 2'-Deoxyuridine and of Thymidine.*

By D. M. BROWN, D. B. PARIHAR, C. B. REESE, and SIR ALEXANDER TODD.

5'-*O*-Acetyl-2'-*O*-toluene-*p*-sulphonyluridine reacts with sodium iodide in hot acetonylacetone, to give 5'-*O*-acetyl-2'-deoxy-2'-iodouridine from which by hydrogenation and deacetylation 2'-deoxyuridine is obtained. The same route starting from 5'-*O*-acetyl-3-β-D-ribofuranosylthymine leads to thymidine. The synthetic deoxyribonucleosides are identical with the naturally occurring compounds.

IN the preceding paper * synthetic approaches to the naturally occurring 2'-deoxyribonucleosides were discussed and it was suggested that methods involving displacement reactions at $C_{(2)}$ of the sugar residue in derivatives of the ribonucleosides might lead to compounds readily convertible into the deoxynucleosides. Preliminary experiments along these lines using uridine derivatives led in fact to 3'-deoxyuridine. 2'-*O*-Toluene-*p*-sulphonyladenosine and 5'-*O*-acetyl-2'-*O*-toluene-*p*-sulphonyluridine were readily available from earlier work [1,2] and we therefore sought to bring about a direct exchange of the toluene-*p*-sulphonyloxy-group in these compounds by iodide, although it has been claimed that the Oldham–Rutherford reaction is not usually applicable to other than toluene-*p*-sulphonates of primary alcohols.[3]

It was found that 5'-*O*-acetyl-2'-*O*-toluene-*p*-sulphonyluridine [2] (I) reacted readily with sodium iodide in hot acetonylacetone and from the reaction mixture a crystalline iodonucleoside was obtained. This was a 2'-deoxy-2'-iodo-compound since hydrogenation over a palladium catalyst gave 5'-*O*-acetyl-2'-deoxyuridine, from which 2'-deoxyuridine (II; R = H) was obtained in high yield. This was identical in all respects with the naturally occurring nucleoside.[4,5]

Whether the intermediate iodo-compound is the *arabo*- (III) or the *ribo*-isomer (IV) has not been established. Its formation might be expected to involve an inversion at position 2', leading to compound (III). However, the substance, like 5'-*O*-acetyl-2'-*O*-toluene-*p*-sulphonyluridine,[2] is readily converted by methanolic ammonia into *O*^{2} : 2'-*cyclo*uridine (V). This suggests either that the compound has the *ribo*-configuration (IV), or that it is (III) and that very easy formation of the intermediate 2' : 3'-anhydrouridine (VI) from it can occur under these mildly basic conditions.[6] The *cyclo*-compound (V) would then be formed by a second inversion.[7] In contrast to the ready reaction between the toluenesulphonate (I) and the iodide ion, Dr. A. M. Michelson found earlier in unpublished experiments that 2'-*O*-methanesulphonyladenosine reacts only very sluggishly with

* Part VI, preceding paper.

[1] Brown, Fasman, Magrath, and Todd, *J.*, 1954, 1448.
[2] Brown, Varadarajan, and Todd, *J.*, 1956, 2388.
[3] Tipson, *Adv. Carbohydrate Chem.*, 1953, **8**, 192; cf., however, Michelson and Todd, *J.*, 1955, 816.
[4] Dekker and Todd, *Nature*, 1950, **166**, 157.
[5] See Brown, Parihar, Reese, and Todd, *Proc. Chem. Soc.*, 1957, 321, for preliminary account.
[6] See Davoll and Lythgoe, *J.*, 1949, 2526, for a possible analogy.
[7] See preceding paper.

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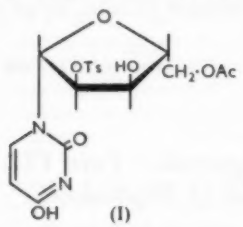
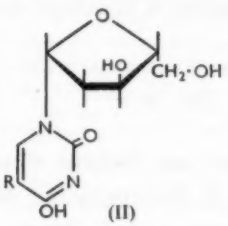
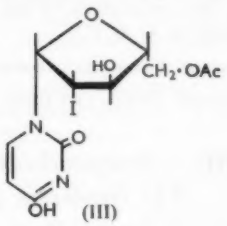
various anions. In addition it was noted [7] that 3′-*O*-toluene-*p*-sulphonyluridine was unaffected by sodium iodide under the usual conditions. If evidence based on ring-opening in 2 : 3-anhydropentofuranosides is relevant to the present discussion, then, other things being equal, nucleophilic displacement at the 3′-position occurs more readily than


(I)


(II)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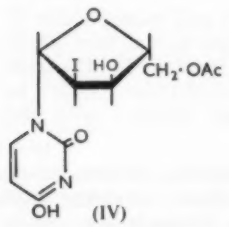
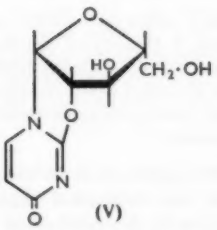
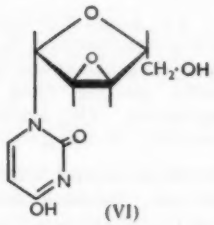

(IV)


(V)


(VI)

at the 2′-position.[8,9] It does appear then that in the present case the uracil 2-carbonyl group may play some part in the displacement reaction. This may become clear when the precise structure of the iodo-compound has been established.

The route evolved for the synthesis of 2′-deoxyuridine was applied to the synthesis of thymidine (II; R = Me). 3-β-D-Ribofuranosylthymine [10] was converted *via* its 2′ : 3′-*O*-*iso*propylidene derivative [11] into the 5′-acetate. It was found that toluene-*p*-sulphonylation proceeded with more difficulty than in the uridine series and that only about 25% conversion could be achieved. Methanesulphonylation was even less satisfactory. Counter-current distribution allowed the complete separation of starting material from 5′-*O*-acetyltoluene-*p*-sulphonylribosylthymine. This could not be crystallised, so it was treated directly with sodium iodide and then the crude material was hydrogenated and deacetylated. The product was then separated by counter-current distribution from minor contaminants which were, on paper chromatographic evidence, unchanged toluene-*p*-sulphonyl derivatives, probably mainly the 3′-isomer. The product was found to be identical with natural thymidine, and it gave on reduction and hydrolysis 2-deoxyribose,[12] identified by paper chromatography.

Recent biochemical work [13] has shown with some certainty that the direct conversion of ribo- into deoxyribo-nucleosides occurs in living organisms, but the mechanism is obscure. Our syntheses can have no direct relevance to possible biosynthetic pathways except in so far as they demonstrate that displacement reactions can be effected at the 2′-position in ribonucleosides. It is possible that, in Nature, displacement of phosphate by hydride ion (or its biochemical equivalent) could occur. Conceivably, too, a 2′-*cyclo*-nucleoside might be an intermediate in the process although on stereochemical grounds we would expect that this would only be possible with the pyrimidine nucleosides. It is of

[8] Mukherjee and Todd, *J.*, 1947, 969; Allerton and Overend, *J.*, 1951, 1480.
[9] Davoll, Lythgoe, and Trippett, *J.*, 1951, 2230.
[10] Fox, Yung, Davoll, and Brown, *J. Amer. Chem. Soc.*, 1956, **78**, 2117.
[11] Griffin and Todd, unpublished work.
[12] Burke, *J. Org. Chem.*, 1955, **20**, 643.
[13] Grossman and Hawkins, *Biochim. Biophys. Acta*, 1954, **26**, 657; Amos and Magasanik, *J. Biol. Chem.*, 1957, **229**, 653.

interest that since the completion of the work described in this paper Shaw and Warrener [14] have reported a synthesis of thymidine from S^2 : 2′-*cyclo*-5-methyl-2-thiouridine in small yield.

Experimental

Evaporations were carried out under reduced pressure. Counter-current distributions were made in the ethyl acetate–water system in an automatic machine (20·5 c.c. phase). Paper chromatograms were run on Whatman No. 1 paper, the R_F values recorded below being for the butan-1-ol–acetic acid–water (5 : 2 : 3 v/v) system.

5′-O-*Acetyl*-2′-*deoxy*-2′-*iodouridine*.—5′-*O*-Acetyl-2′-*O*-toluene-*p*-sulphonyluridine [2] (5·36 g.) and dry sodium iodide (5·36 g.) were dissolved in freshly distilled acetonylacetone (53 c.c.) and the solution was heated for 2·75 hr. on the water-bath with exclusion of moisture, then cooled. Sodium toluene-*p*-sulphonate (2·2 g.; 96%) was removed by filtration, and washed with acetone and ether. Filtrate and washings were evaporated, finally at 100° *in vacuo*, yielding a thick red syrup which was dissolved in water (20 c.c.). A few crystals of sodium thiosulphate were added, then the solution was submitted to counter-current distribution (80 transfers). The contents of tubes 50—70 which contained a single substance R_F 0·78 were evaporated to a glass (3·74 g.), which crystallised from ethanol (5 c.c.)–ether (2 c.c.) as colourless needles. Recrystallised from dry ethanol it gave needles (2·22 g.), m. p. 167° (Found, in material dried at 85°/0·1 mm. for 4 hr. over P_2O_5: C, 33·35; H, 3·3; N, 6·8. $C_{11}H_{13}O_6N_2I$ requires C, 33·33; H, 3·3; N, 7·1%), $\lambda_{max.}$ 259 mμ (ε 10,770), $\lambda_{min.}$ 229 mμ (ε 2690) in 95% EtOH.

The substance (25 mg.) was set aside with half-saturated methanolic ammonia. After 7 hr. at room temperature, paper chromatography (propan-2-ol–1% ammonium sulphate system) showed the presence of O^2 : 2′-*cyclo*uridine (R_F 0·68) and 3-β-D-arabofuranosyl*iso*cytosine (R_F 0·60), the starting material having disappeared. The former was isolated after 3 days as needles, m. p. 234—235° undepressed on admixture with an authentic specimen of O^2 : 2′-*cyclo*uridine; infrared spectra were identical.

5′-O-*Acetyl*-2′-*deoxyuridine*.—The above iodo-compound (0·325 g.) was dissolved in 50% ethanol (30 c.c.), sodium acetate (0·41 g.) added, and the solution hydrogenated over 5% palladium–barium sulphate (0·29 g.) at room temperature and pressure. Reaction was complete in 4 hr.; after removal of catalyst and solvent the residue was dissolved in water (10 c.c.), and the solution extracted three times with ethyl acetate. The extract was taken to dryness and the syrup dissolved in dry ethanol (5 c.c.). After several weeks in the cold 5′-O-*acetyl*-2′-*deoxyuridine* separated in thick rods which shrank at 90° and melted at 96°; it had R_F 0·68 (Found, in material dried at 40°/0·1 mm.: C, 49·1; H, 5·4; N, 10·7. $C_{11}H_{14}O_6N_2$ requires C, 48·9; H, 5·2; N, 10·4%), and $\lambda_{max.}$ 261 mμ (ε 9550), $\lambda_{min.}$ 230 mμ (ε 1960) in 95% EtOH.

2′-*Deoxyuridine*.—5′-*O*-Acetyl-2′-deoxy-2′-iodouridine (1·6 g.) was dissolved in 50% ethanol (50 c.c.), ammonia added to pH 9, and the solution hydrogenated over palladium–barium sulphate (1·60 g.). Uptake of hydrogen ceased before the theoretical volume had been taken up, so the solution was again brought to pH 9 and a further quantity of catalyst (1·0 g.) was added. Hydrogenation was complete in 24 hr. and after removal of catalyst and solvent the residual gum, which contained 2′-deoxyuridine (R_F 0·54) and its acetate (R_F 0·68), was dissolved in water (10 c.c.), and the solution extracted with ethyl acetate continuously for 4 hr. Evaporation of the ethyl acetate extract gave a glass which was treated with half-saturated methanolic ammonia (100 c.c.) for 8 hr. at room temperature. Removal of solvent and crystallisation of the residue from absolute ethanol (5 c.c.) gave 2′-deoxyuridine. Recrystallised twice from the same solvent this formed stout needles (0·76 g.), m. p. 167° undepressed on admixture with the natural substance (Found: C, 47·2; H, 5·3; N, 12·6. Calc. for $C_9H_{12}O_5N_2$: C, 47·4; H, 5·3; N, 12·3%). Its infrared and ultraviolet spectra and characteristics on paper chromatography and electrophoresis were identical with those of natural 2′-deoxyuridine.[4]

5′-O-*Acetyl*-3-β-D-*ribofuranosylthymine*.—2′ : 3′-*iso*Propylidene-3-β-D-ribofuranosylthymine [11] (14·3 g.) was dissolved in dry pyridine (100 c.c.), acetic anhydride (20 c.c.) was added, and the mixture left for 4 hr. at room temperature. Ethanol (200 c.c.) was added with cooling and after 30 min. solvents were removed. The product, a pale yellow glass (16·2 g.) which gave one spot on chromatograms (R_F 0·90), was presumably the 5′-*O*-acetyl-2′ : 3′-*iso*propylidene derivative. It (15 g.) was dissolved in 20% acetic acid (300 c.c.), and the solution

[14] Shaw and Warrener, *Proc. Chem. Soc.*, 1958, 81.

boiled under reflux for 1 hr. The solvent was removed and the residual gum was subjected to counter-current distribution (94 transfers), to remove traces of uncharged starting material and ribosylthymine. The contents of tubes 8—23 were pooled and evaporated. The residual 5′-*acetate* crystallised from ethanol as needles (11·1 g.), m. p. 95°, R_F 0·67 (Found: C, 48·0; H, 5·5; N, 9·3. $C_{13}H_{16}O_7N_2$ requires C, 48·0; H, 5·3; N, 9·3%), $\lambda_{max.}$ 265 mμ (ε 8675), $\lambda_{min.}$ 234 mμ (ε 1870) in 95% EtOH.

Thymidine (2′-*Deoxy*-3-β-D-*ribofuranosylthymine*).—The above 5′-*O*-acetyl compound (5·0 g.) was dissolved in dry pyridine (30 c.c.), and toluene-*p*-sulphonyl chloride (3·49 g., 1·1 mol.) added. The clear solution was set aside overnight at room temperature. Ethanol (100 c.c.) was added and solvents were then removed under reduced pressure. Water (20 c.c.) was added to the residual syrup, and after 6 hr. in the cold the solution was adjusted to pH 7 with sodium hydroxide and then extracted with ethyl acetate (4 × 200 c.c.). The aqueous phase contained an ultraviolet-absorbing substance (R_F 0·34), probably a *cyclo*nucleoside. The ethyl acetate extract, on being set aside, deposited some 5′-*O*-acetylribofuranosylthymine, from which it was decanted. After removal of solvent the glass (2·4 g.) was subjected to counter-current distribution (85 transfers). The contents of tubes 3—14 yielded pure 5′-*O*-acetylribofuranosylthymine (total recovered, 2·4 g.). Tubes 72—85 gave a gum (1·3 g.) showing two spots on chromatograms which were periodate-negative, probably corresponding to 2′(and 3′)-toluene-*p*-sulphonyl derivatives.

The gum from tubes 72—85 was dried thoroughly, then heated at 100° with sodium iodide (1·28 g.) in acetonylacetone (12·8 c.c.) for 3 hr. The red solution was cooled, filtered from sodium toluene-*p*-sulphonate (0·233 g.; theor. 0·50 g.), and evaporated. The residual syrup was dissolved in water (10 c.c.) and treated with a little sodium thiosulphate, and the solution continuously extracted with ethyl acetate for 3 hr. The ethyl acetate (100 c.c.) extract was washed with water (2 × 25 c.c.), then evaporated to a syrup (1·25 g.). This material showed an intense spot on paper chromatograms (R_F 0·79), giving a pink colour with the cysteine–sulphuric acid spray reagent, probably due to 5′-*O*-acetyl-2′-iodothymidine together with minor impurities (probably 3′-*O*-toluene-*p*-sulphonyl derivatives) at R_F 0·85 and 0·71.

The syrup and sodium acetate (1·5 g.) dissolved in 50% ethanol (50 c.c.) were hydrogenated over palladium–barium sulphate (1·3 g.). Reaction ceased after uptake of 10 c.c. of hydrogen. Fresh catalyst (1·0 g.) was added and hydrogenation was completed in 8 hr. The residue after removal of catalyst and solvent was dissolved in water (10 c.c.) and continuously extracted with ethyl acetate for 4 hr. The extract was taken to dryness and the yellow syrup dissolved in half-saturated methanolic ammonia (50 c.c.). After 24 hr. the solvent was removed and the residue, which contained thymidine as a major component (R_F 0·62; cysteine-positive) together with two minor components (R_F 0·82, 0·70), was subjected to counter-current distribution (89 transfers). Tubes 1—15 contained thymidine (crude yield 263 mg.), a trace of ultraviolet-absorbing impurity (R_F 0·70) being present in tubes 1—4. The residual gummy crystals from tubes 5—15 were recrystallised thrice from absolute ethanol (4 c.c.) and formed needles, m. p. 182—185° undepressed on admixture with natural thymidine (Found: C, 49·3; H, 5·6. Calc. for $C_{10}H_{14}O_5N_2$: C, 49·6; H, 5·8%). The infrared spectrum (in Nujol and in hexachlorobutadiene) of the product was identical with that of thymidine. Paper-chromatographic (R_F 0·62) and electrophoretic behaviour were also the same; the product, like thymidine, gave a negative periodate reaction, a purple spot with Dische's diphenylamine reagent, and a persistent deep pink colour with the cysteine–sulphuric acid spray.[15]

A portion (10 mg.) of the syrup from tubes 1—4 was reduced and then hydrolysed,[12] and the sugar obtained compared with all the other 2- and 3-deoxypentoses [7] by chromatography. When chromatograms were sprayed with the aniline phthalate reagent the material showed a major component corresponding to 2-deoxyribose in colour (yellow-brown) and R_F (0·39) and a minor one (pink, R_F 0·45) of 3-deoxyribose [butan-1-ol–ethanol–water (4 : 1 : 5) system]. Paper electrophoresis led to the same conclusion.

Grateful acknowledgment is made of a Senior Studentship of the Royal Commission for the Exhibition of 1851 (to C. B. R.) and an Overseas Scholarship of the Ministry of Education, Government of India (to D. B. P.).

University Chemical Laboratory, Cambridge. [*Received, April 8th,* 1958.]

[15] Wyatt, in "The Nucleic Acids," Ed. Chargaff and Davidson, 1955, Vol. I, 243.

617. *Studies on Phosphorylation. Part XVIII.* Base-inhibited Hydrogenolysis in the Selective Debenzylation of Phosphoric and Phosphoramidic Esters.*

By V. M. Clark, G. W. Kirby, and Sir Alexander Todd.

The hydrogenolytic debenzylation of the neutral esters of phosphoric, phosphoramidic, and certain *N*-substituted phosphoramidic acids is subject to inhibition by a variety of bases. From this a convenient method of selective debenzylation has been developed and is exemplified by the preparation of a number of *N*-substituted benzyl hydrogen phosphoramidates.

Investigation of the phosphorylation of alcohols under mild conditions led to the development of dibenzyl phosphorochloridate as a convenient reagent, the two benzyl groups of the initially formed triester being removed subsequently by hydrogenolysis.[1] These triesters can provide suitable starting materials for pyrophosphate synthesis by the selective removal of one of the benzyl groups by means of a tertiary amine [2] or a salt containing a polarisable anion,[3] and these methods have been applied in a variety of syntheses of pyro- and poly-phosphates.[4]

In the preliminary work on simple alcohols [1] it was noted that hydrogenolysis of dibenzyl *iso*pentyl phosphate with a palladised charcoal catalyst in the presence of *N*-*n*-butylpiperidine was slow, but gave the *mono*debenzylated product, isolated as a silver salt. Inhibition of hydrogenation has been observed in a number of systems. Thus, Naves [5] showed that the hydrogenolysis of esters of benzyl alcohol with Raney nickel was generally rapid and complete in ethanol but much slower in dioxan or in the presence of dimethylaniline, and Baltzly and his co-workers [6] have indicated that such hydrogenolyses are inhibited by alkali and by free amines of basic strength above a certain minimum. Maxted and Walker [7] and, more recently, Devereux, Payne, and Peeling [8] have demonstrated that hydrogenation of aromatic amines with a platinum oxide catalyst is inhibited by the amine itself and its reduction product, while Maxted and Biggs [9] have recorded the deactivating effect of dry ammonia upon platinum in the hydrogenation of *cyclo*hexene.

The effect of alkali on the activity of the catalyst varies in the different examples studied [10] and depends to a large extent on the degree of subdivision, a coarse-grained, relatively inactive catalyst often being far more sensitive to poisoning than a finely divided, highly active one.[11] Baltzly and Buck,[6] following the work of Hartung and Crossley,[12] confirmed the superiority of palladium catalysts for hydrogenolytic debenzylation and we now record a method for the selective debenzylation of esters of phosphoric and a number of *N*-substituted phosphoramidic acids using such catalysts in the presence of bases.[13]

In the presence of one molecular equivalent of 4-methylmorpholine, the rate of hydrogenation of tribenzyl phosphate in presence of 10% palladised charcoal at room

* Part XVII, *J.*, 1958, 2968.

[1] Atherton, Openshaw, and Todd, *J.*, 1945, 382; cf. Zervas, *Naturwiss.*, 1939, **27**, 317.
[2] Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815.
[3] Clark and Todd, *J.*, 1950, 2030; Cremlyn, Kenner, Mather, and Todd, *J.*, 1958, 528.
[4] Cf. Todd, *Proc. Roy. Soc.*, 1954, *A*, **226**, 70.
[5] Naves, *Helv. Chim. Acta*, 1944, **27**, 261.
[6] Baltzly and Buck, *J. Amer. Chem. Soc.*, 1943, **65**, 1984; Baltzly and Phillips, *ibid.*, 1946, **68**, 261.
[7] Maxted and Walker, *J.*, 1948, 1093.
[8] Devereux, Payne, and Peeling, *J.*, 1957, 2845.
[9] Maxted and Biggs, *J.*, 1957, 3844; cf. Bremner, *Research*, 1948, **1**, 281.
[10] Reasenberg, Lieber, and Smith, *J. Amer. Chem. Soc.*, 1939, **61**, 384.
[11] Maxted and Evans, *J.*, 1937, 603.
[12] Hartung and Crossley, *J. Amer. Chem. Soc.*, 1934, **56**, 158.
[13] Cf. Todd, *Angew. Chem.*, 1948, **60**, 69; Vollmar and Cramer, *ibid.*, 1957, **69**, 104.

XUM

temperature and atmospheric pressure was greatly reduced, but there was no point of inflexion in the curve of hydrogen uptake against time which might correspond to the selective removal of one benzyl group. On increasing the amount of amine present, progressive retardation after the removal of one benzyl group was observed. Thereafter, use of a variety of bases gave similar effects, as illustrated in Fig. 1; for example, in the presence of 5 mols. of sodium methoxide hydrogenation of tribenzyl phosphate gave a 72% yield of dibenzyl hydrogen phosphate.

With dibenzyl phosphoramidate, selective debenzylation was performed in similar fashion, base again having a marked effect on both the rate of uptake and the total hydrogen absorption (Fig. 2). By using two mols. of triethylamine as inhibitor, it was possible, after hydrogenation, to isolate benzyl hydrogen phosphoramidate in high yield and the method has been extended to the preparation of the corresponding *N*-benzyl, *N*-1-phenylethyl, *N*-*cyclo*hexyl, *N*-phenyl, *N*-*p*-hydroxyphenyl, and *N*-*p*-tolyl derivatives. Earlier preparations of the monobenzyl esters of various *N*-substituted phosphoramidic

FIG. 1. FIG. 2.

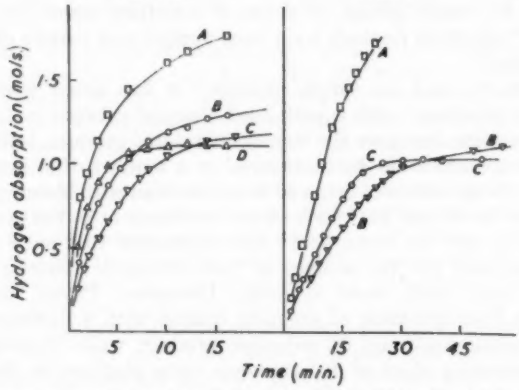


FIG. 1. *Hydrogenolysis of tribenzyl phosphate* (1·23 *g.*) *in ethanol* (110 *ml.*) *with* 10% Pd–C *catalyst* (200 *mg.*) *at* 12·5° *in the presence of various bases* (5 *mols. each of*; *A*, *morpholine*; *B*, cyclo*hexylamine*; *C*, 4-*methylmorpholine*; *D*, *sodium methoxide*).

FIG. 2. *Hydrogenolysis of dibenzyl phosphoramidate* (510 *mg.*) *in ethanol* (30 *ml.*) *with* 10% Pd–C *catalyst* (50 *mg.*) *at* 20° *in the presence of varying amounts of base* (*A*, *no base*; *B*, 1 *mol. of triethylamine*; *C*, 2 *mols. of triethylamine*).

acids for use in pyrophosphate synthesis [14] had been accomplished by anionic debenzylation of the corresponding dibenzyl ester, but the present method appears to be more convenient. Anionic debenzylation of phosphoramidic, as opposed to phosphoric, esters requires not only somewhat forcing conditions but usually that the product should be precipitated during the reaction, thereby displacing the equilibrium in the desired direction.[3] Such a separation of the product is by no means invariable; for example, after treatment with sodium iodide in ethyl methyl ketone under reflux for 1 hr. dibenzyl *N*-*cyclo*hexylphosphoramidate was recovered in 85% yield, no precipitation of product having occurred.

Of the palladium catalysts used, palladium black [15] was much less susceptible to inhibition than palladised charcoal, possibly owing to its greater subdivision. Dibenzyl phosphoramidate was rapidly and completely debenzylated by hydrogenation in presence of palladium black, and Zervas and Katsoyannis [16] have recorded analogous results in their preparation of *N*-phosphorylated amino-acids from the corresponding *P*-dibenzyl esters.

[14] Clark, Kirby, and Todd, *J.*, 1957, 1497.
[15] Wieland, *Ber.*, 1912, **45**, 484.
[16] Zervas and Katsoyannis, *J. Amer. Chem. Soc.*, 1955, **77**, 5351.

Hydrogenolysis of esters may be akin to protonolysis, the relative ease of removal, benzyl ≫ *cyclo*hexyl > *sec.*-butyl > ethyl ≫ methyl,[17] supporting this view. The reaction rate would then depend on the surface concentration of protons, and hydrogenolysis might be slowed down or stopped by introduction of a base. However, although the rate of hydrogen uptake is reduced on addition of base, the initial rate in the presence of 2 mols. of amine is greater than in the presence of 1 mol. (Fig. 2) and this has been our experience during several years. It seems therefore that base affects, not only the stationary work function of the catalyst surface,[18] but also the adsorption–desorption equilibrium at that surface, the monodebenzylated material being desorbed rapidly under the conditions used. Our work throws little light on the mechanism of the catalysis, though the conditions are readily reproducible; however, it provides a very satisfactory preparative method of partial debenzylation.

Experimental

Palladised Charcoal Catalyst.[19]—Charcoal (Karbak H.T. 20) was heated under reflux for 5 hr. with a 1 : 1 v/v mixture of concentrated hydrochloric acid and water to remove traces of metals and, after washing with distilled water until nickel-free, was dried at 110° for 12 hr. A solution of palladium chloride (2 g.) in N-hydrochloric acid (25 ml.) at 40° was cooled and diluted with water (250 ml.). The charcoal (20 g.) was added and the palladium reduced on to the support by shaking the whole in hydrogen for 1 hr. at room temperature and atmospheric pressure (uptake, 500 ml., theor. 270 ml.). The catalyst was filtered off, washed until free from chloride ion, and dried at 80° for 24 hr.

Effect of Various Bases on the Hydrogenation of Tribenzyl Phosphate.—Aliquot parts (100 ml.) of tribenzyl phosphate (12·3 g.) in dry ethanol (1 l.) were used for the various hydrogenations. A further small volume (10 ml.) of ethanol was used in each case for the introduction of the catalyst (200 mg.) and to enable a correction to be made for the volume of base added. Before each hydrogenation the catalyst was saturated with hydrogen at atmospheric pressure.

The results obtained by use of 5 mols. of *cyclo*hexylamine, morpholine, 4-methylmorpholine, or sodium methoxide are indicated in Fig. 1. To the solution from the hydrogenation in presence of alkoxide, 3N-hydrochloric acid (25 ml.) was added and the mixture extracted with chloroform (2 × 25 ml.). The extract was shaken with 10% aqueous sodium hydroxide (25 ml.) and the alkaline layer then acidified with dilute sulphuric acid and again extracted with chloroform (3 × 25 ml.). Evaporation gave an oil which crystallised on addition of ether. Recrystallisation from ether gave dibenzyl hydrogen phosphorate (670 mg., 72%), m. p. 78°, undepressed in admixture with an authentic specimen.[20]

Effect of Triethylamine on the Hydrogenation of Dibenzyl Phosphoramidate.—The rates of hydrogen uptake in the hydrogenation of dibenzyl phosphoramidate with 10% palladised charcoal in the absence of base and in the presence of 1 and 2 mols. of triethylamine are compared in Fig. 2. When palladium black [16] was used as catalyst, complete debenzylation occurred even in the presence of 2 mols. of triethylamine (cf. ref. 16).

Benzyl Hydrogen Phosphoramidate.—Dibenzyl phosphoramidate (3·0 g.) in ethanol (75 ml.) containing triethylamine (2·2 g., 2 mol.) was hydrogenated over 10% palladised charcoal (300 mg.) at room temperature and atmospheric pressure. After 45 min. the suspension was filtered and the filtrate treated with a solution from sodium (0·25 g., 1 mol.) in a little ethanol. The precipitated sodium salt (1·93 g.) was kept at 5° for 1 hr., collected, washed with ethanol and ether, and dried *in vacuo*. *Sodium benzyl phosphoramidate* crystallised from aqueous ethanol as colourless plates (Found, after drying over P_2O_5 at 20°/0·1 mm.: C, 40·0; H, 4·5; N, 6·7. $C_7H_9O_3NPNa$ requires C, 40·2; H, 4·3; N, 6·7%).

The crude sodium salt (0·50 g.) was dissolved in water (3 ml.), filtered and treated with ethanol (1 ml.) followed by 3N-hydrochloric acid (1 ml.). Benzyl hydrogen phosphoramidate separated immediately as plates, which, after 15 min. at 0°, were collected, washed with a little ice-cold water, and dried (P_2O_5) (yield 0·29 g., 50%). The infrared spectrum between 4000 and 650 cm.$^{-1}$ was identical with that of Clark and Todd's [3] specimen.

[17] Adkins and Folkers, *J. Amer. Chem. Soc.*, 1932, **54**, 1145.
[18] Dowden, *J.*, 1950, 242.
[19] Cf. *Org. Synth.*, Coll. Vol. III, 1955, p. 685.
[20] Lossen and Köhler, *Annalen*, 1891, **262**, 211.

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Benzyl Hydrogen N-cyclo*Hexylphosphoramidate.*—Dibenzyl *N-cyclo*hexylphosphoramidate [21] (0·50 g.) in ethanol (20 ml.) containing triethylamine (0·28 g., 2 mol.) was hydrogenated over 10% palladised charcoal (50 mg.) at room temperature and atmospheric pressure, the hydrogen uptake being complete after 50 min. After evaporation of solvent, the residue was shaken with water (20 ml.) and 10% sodium hydroxide solution added until the product had dissolved. Catalyst was filtered off and the filtrate acidified with 3N-hydrochloric acid, benzyl hydrogen *N-cyclo*hexyl phosphoramidate being precipitated. After 1 hr. at 5° the product was collected, washed with water, and dried (P_2O_5). Recrystallisation from ethyl acetate gave needles (0·27 g., 72%), m. p. 96—100° undepressed on admixture with an authentic specimen.[14]

Benzyl Hydrogen N-*Benzylphosphoramidate.*—Dibenzyl *N*-benzylphosphoramidate [21] (0·66 g.) was monodebenzylated under the conditions described above for the *N-cyclo*hexyl derivative. The crude benzyl hydrogen *N*-benzylphosphoramidate (0·44 g.) was recrystallised from ethyl acetate, forming prisms (0·27 g., 54%), m. p. 98—100° (Found: C, 60·5; H, 6·0; N, 5·0. Calc. for $C_{14}H_{16}O_3NP$: C, 60·6; H, 5·8; N, 5·1%).

Benzyl Hydrogen N-1-*Phenylethylphosphoramidate.*—Dibenzyl *N*-1-phenylethylphosphoramidate [21] (0·685 g.) was debenzylated as in the preceding example. The aqueous alkaline extract of the reaction product, acidified with 3N-hydrochloric acid, gave *benzyl hydrogen* N-1-*phenylethylphosphoramidate* as needles which, after 1 hr. at 5°, were collected, washed with water, and dried *in vacuo* (P_2O_5) (yield 0·46 g., 88%) (Found: C, 61·8; H, 6·2; N, 4·9. $C_{15}H_{18}O_3NP$ requires C, 61·9; H, 6·2; N, 4·8%). Recrystallised from ethyl acetate, these had m. p. 88—92°.

Benzyl Hydrogen N-*Phenylphosphoramidate.*—Dibenzyl *N*-phenylphosphoramidate [21] (0·65 g.) was hydrogenated in the presence of triethylamine (0·37 g., 2 mols.). After 40 min. hydrogenation was discontinued, the suspension filtered, and the filtrate treated with sodium (0·042 g., 1 mol.) dissolved in ethanol (10 ml.). Evaporation yielded crude *sodium benzyl* N-*phenylphosphoramidate* (0·50 g.). Recrystallised from ethanol–ether, the salt * formed needles (0·38 g., 68%) (Found: C, 51·5; H, 4·8; N, 5·0. $C_{13}H_{13}O_3NPNa,H_2O$ requires C, 51·5; H, 4·9; N, 4·6%). Treatment of the salt (100 mg.) in water (5 ml.) with excess of 3N-hydrochloric acid at 5° precipitated *benzyl hydrogen* N-*phenylphosphoramidate* (80 mg.) (Found: C, 59·1; H, 5·6; N, 5·55. $C_{13}H_{14}O_3NP$ requires C, 59·3; H, 5·3; N, 5·3%). Recrystallisation from aqueous ethanol was accompanied by decomposition; the acid then formed colourless plates, m. p. 120—122° (Found: C, 58·7; H, 5·7; N, 5·5%).

Benzyl Hydrogen N-p-*Tolylphosphoramidate.*—As in the previous example, *sodium benzyl* N-p-*tolylphosphoramidate* (0·49 g.) was obtained from the dibenzyl ester [21] (0·66 g.). Recrystallised from ethanol–ether, the salt formed needles (0·37 g., 69%) (Found: C, 54·1; H, 4·9; N, 4·8. $C_{14}H_{15}O_3NPNa,\frac{1}{2}H_2O$ requires C, 54·6; H, 5·2; N, 4·5%). Treatment of the salt (100 mg.) with 3N-hydrochloric acid gave the free *acid* (65 mg.) as needles, m. p. 113—116° (Found: C, 60·3; H, 5·9; N, 5·2. $C_{14}H_{16}O_3NP$ requires C, 60·6; H, 5·8; N, 5·1%).

Dibenzyl N-p-*Hydroxyphenylphosphoramidate.*—*p*-Aminophenol (1·1 g.) and triethylamine (2 ml.) in dry acetone (50 ml.) were mixed with dibenzyl phosphonate (2·6 g.) in carbon tetrachloride [21] (10 ml.) and left at room temperature for 20 hr. Precipitated triethylammonium chloride was removed and the filtrate evaporated, the residue being taken up in chloroform (20 ml.). The solution was washed with 3N-hydrochloric acid (20 ml.) and water (2 × 20 ml.); during each washing a crystalline product separated at the interface. This was collected and the washed chloroform layer kept at 5° until no more material separated (total yield, 1·60 g.). After drying (Na_2SO_4), the chloroform solution was concentrated (to 10 ml.) and light petroleum added. A second crop of product (0·40 g.) separated. Recrystallisation from chloroform–light petroleum gave *dibenzyl* N-p-*hydroxyphenylphosphoramidate* as plates (1·75 g., 47%), m. p. 118—120° (Found: C, 64·9; H, 5·65; N, 4·0. $C_{20}H_{20}O_4NP$ requires C, 65·0; H, 5·4; N, 3·8%).

Acetylation of the dibenzyl ester with acetic anhydride–pyridine gave the O-*acetate*, which, recrystallised from aqueous ethanol, had m. p. 86—87°, $\nu_{max.}$ 1760 cm.$^{-1}$ (Nujol mull) (Found: C, 64·0; H, 5·6. $C_{22}H_{22}O_5NP$ requires C, 64·2; H, 5·4%).

Benzyl Hydrogen N-p-*Hydroxyphenylphosphoramidate.*—The dibenzyl ester (300 mg.) in ethanol (20 ml.) was hydrogenated in the presence of triethylamine (250 mg., 3 mols.)

* Also prepared by Dr. D. H. Marrian (personal communication) using thiocyanate ion (cf. ref. 3).

[21] Atherton, Openshaw, and Todd, *J.*, 1945, 660.

XUM

and 10% palladised charcoal (20 mg.). After 25 min. the hydrogenation was interrupted and the solution filtered. Evaporation of the filtrate left a gum which was dissolved in water (5 ml.). Treatment with excess of N-hydrochloric acid precipitated *benzyl hydrogen* N-p-*hydroxyphenylphosphoramidate*, which was washed sparingly with water, dissolved in a minimum of 0·1N-sodium carbonate, and reprecipitated with N-hydrochloric acid as plates (121 mg., 52%). After further washing, the product was dried at room temperature *in vacuo* (P_2O_5), then having m. p. 126—128° (Found: C, 54·9; H, 5·4; N, 5·1. $C_{13}H_{14}O_4NP,\frac{1}{2}H_2O$ requires C, 54·2; H, 5·2; N, 4·9%).

Grateful acknowledgment is made to the Department of Scientific and Industrial Research for a Maintenance Allowance and to Gonville and Caius College for the award of the Dunlop Studentship (to G. W. K.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, April 23rd,* 1958.]

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618. *Steric Effects in 2 : 2'-Bridged Diphenyls with a Heterocyclic Bridging Ring. Part I. Optically Active Dihydrodibenzazepines.*

By SHAKTI R. AHMED and D. MURIEL HALL.

2 : 2'-Bisbromomethyl-6 : 6'-dinitrodiphenyl has been condensed with (−)-ephedrine and the resulting quaternary bromide separated into two diastereoisomers. Hofmann degradation of the two bromides gave (−)- and (+)-2 : 7-dihydro-1-methyl-4' : 1''-dinitro-3 : 4-5 : 6-dibenzazepine with $[\alpha]_{5461}^{19}$ −1343° and +1333° respectively. The cyclic amines are optically stable in benzene solution up to about 100° and racemise slowly at 125°. Similar condensation of 2 : 2'-bisbromomethyl-6 : 6'-difluorodiphenyl with (−)-ephedrine, followed by Hofmann degradation of the diastereoisomeric bromides, gave optically active (but probably not optically pure) (−)- and (+)-4' : 1''-difluoro-2 : 7-dihydro-1-methyl-3 : 4-5 : 6-dibenzazepine. The hydrochlorides of the fluoro-amines racemise in aqueous acid at 80° with a half-life of 6·5 hr.

OPTICAL activity has been demonstrated in compounds of the types (I) and (II) only when *ortho*-substituents [or fused benzene rings as in (III) and (IV)] are present.[1,2] In view of the high optical stability and very low specific rotation of the dimethoxy-compound (I*a*) ($[\alpha]_{5461}^{22}$ +4·0° and −3·8°), this failure to resolve compounds of types (I*b*) and (II), in which R = H, was originally attributed to experimental difficulties rather than to lability of configuration. Support for this view came from the greatly increased specific rotations (presumably associated with their different light-absorbing properties) of the dinaphthyl compounds (III) and (IV) which have $[\alpha]_{5461}^{20}$ +306·5° and +205·3° respectively.

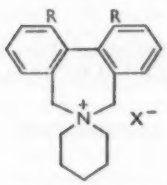
However, more recent work on diphenyls with other types of bridging rings suggests that in the absence of other *ortho*-substituents compounds with a bridge of three or four atoms possess only low optical stability.[3,4,5] At the same time further evidence of the low optical rotation associated with this type of structure has been obtained. Thus compound (V) [3] had $[\alpha]_D^{32\cdot5}$ +2·25° and compound (VI) [4] had $[\alpha]_D^{25}$ +3·1°.

In order to extend our knowledge of the configurational stability of 2 : 2'-bridged diphenyls we have therefore begun a study of the effects of various *ortho*-substituents on the optical stability of compounds of the types (I) and (II). At the same time it seemed desirable to facilitate the detection of optical resolution or asymmetric transformation, if either of them occurred, by using compounds of higher specific rotation. With this in

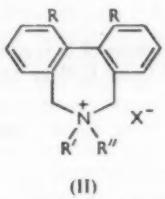
[1] Beaven, Hall, Lesslie, and Turner, *J.*, 1952, 854.
[2] Hall and Turner, *J.*, 1955, 1242.
[3] Iffland and Siegel, *J. Org. Chem.*, 1956, **21**, 1056.
[4] Truce and Emrick, *J. Amer. Chem. Soc.*, 1956, **78**, 6130.
[5] (*a*) Mislow, *Trans. New York Acad. Sci.*, 1957, [2], **19**, 298; (*b*) Dvorken, Smyth, and Mislow, *J. Amer. Chem. Soc.*, 1958, **80**, 486.

XUM

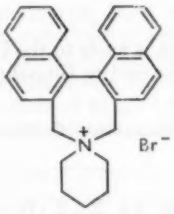
view we selected nitro-groups as suitable *ortho*-substituents for preliminary study, as their bathochromic effect on the electronic absorption bands might be expected to increase the optical rotatory power in the region in which it can most easily be measured. They have the further advantage of being a suitable starting point for the introduction of other groups and, in addition, a certain amount is already known about their steric [6] and other [6,7] effects on the optical stability of *unbridged* diphenyls.



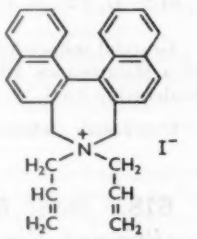
(I*a*) : R = OMe, X = I.
(I*b*) : R = H, X = I.
(I*c*) : R = NO_2, X = I.
(I*d*) : R = F, X = I.



(II)



(III)



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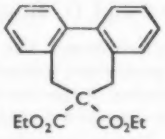

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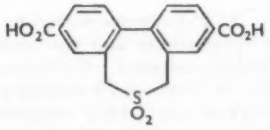
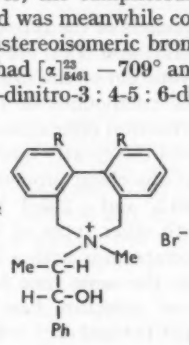
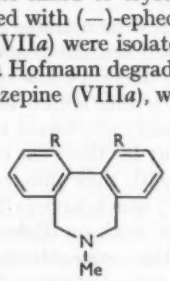


(VI)

Accordingly 2 : 2′-dimethyl-6 : 6′-dinitrodiphenyl was prepared and was brominated by *N*-bromosuccinimide in the presence of benzoyl peroxide, a method used by Wenner [8] for other ditolyls. Interaction of the resulting 2 : 2′-bisbromomethyl-6 : 6′-dinitrodiphenyl * with piperidine gave the *spiro*-piperidinium compound (I*c*) which was isolated as the iodide. However, the camphorsulphonate failed to crystallise for nearly a year. The dibromo-compound was meanwhile condensed with (−)-ephedrine and, after repeated crystallisation, two diastereoisomeric bromides (VII*a*) were isolated. The one which was less soluble in ethanol had $[\alpha]_{5461}^{23}$ −709° and by a Hofmann degradation gave (−)-2 : 7-dihydro-1-methyl-4′ : 1″-dinitro-3 : 4-5 : 6-dibenzazepine (VIII*a*), with $[\alpha]_{5461}^{19}$ −1343°. The

(VII*a*) : R = NO_2
(VII*b*) : R = F





(VIII*a*) : R = NO_2
(VIII*b*) : R = F

quaternary bromide which was more soluble in ethanol, had $[\alpha]_{5461}^{18}$ +689° and, in a similar way, gave the (+)-azepine with $[\alpha]_{5461}^{19}$ +1333°.

The azepine was optically stable in benzene solution up to about 100°. The yellow

* Shortly after we had first made this compound its preparation by a different method was announced by Iffland and Siegel [5] and by Mislow and Newman.[9]

[6] Stanley and Adams, *J. Amer. Chem. Soc.*, 1930, **52**, 1200; Adams and Yuan, *Chem. Rev.*, 1933, **12**, 261; and many other papers.
[7] Brooks, Harris, and Howlett, *J.*, 1957, 1934.
[8] Wenner, *J. Org. Chem.*, 1952, **17**, 523.
[9] Mislow and Newman, *J. Amer. Chem. Soc.*, 1957, **79**,1769.

XUM

solution became very dark when heated at 110° in the air and it was therefore not possible to follow the racemisation by direct observation of a solution in a jacketed polarimeter tube at a suitable temperature. Instead, a solution of the azepine in benzene was heated in a number of sealed tubes in a thermostat-controlled oil-bath, and tubes were withdrawn at suitable intervals for polarimetric examination. In this way the dinitroazepine in benzene solution was found to have a half-life of 16 hr. at 125° and of 2·6 hr. at 145°, whence the activation energy is 30 kcal. mole^{-1}. Rather surprisingly the dinitroazepine appears to be much less optically stable than the dimethoxyazepinium compound (I*a*), which was only partly racemised after 8 hr. in boiling *cyclo*hexanol solution (160°).[1] However, the difference in the valency state of the nitrogen atom in the two compounds may well affect their relative optical stabilities, as may the alteration in type of solvent. To test this, the methiodide (II; R = NO_2, R′ = R″ = Me, X = I) of the (−)-dinitroazepine was made. It racemised in acetone solution (sealed tubes) at 145° with a half-life of 4·75 hr. It is thus nearly twice as optically stable as the tertiary amine at that temperature, but still not as stable as the quaternary dimethoxy-compound.

The slight steric effect of fluorine, compared with that of any other (necessarily larger) atom or group, is apparent from extensive studies[10] of optical stabilities in non-bridged hindered diphenyls and also from recent spectroscopic work.[11] We therefore prepared 2 : 2′-difluoro-6 : 6′-dimethyldiphenyl[12] and brominated it with peroxide-catalysed *N*-bromosuccinimide. In this case the dibromo-compound failed to crystallise and was condensed without isolation with piperidine, giving the salt (I*d*), and with (−) ephedrine, giving the salt (VII*b*). The latter was crystallised from ethanol and the less soluble bromide obtained as needles with $[\alpha]_{5461}^{18\cdot5}$ +50°. Its diastereoisomer crystallised from aqueous ethanol in hydrated cubes with $[\alpha]_{5461}^{18\cdot5}$ −55°. In view of the expected optical instability of these compounds, Hofmann degradation was carried out at the lowest temperature practicable, *viz.*, about 70°. The resulting azepines (VIII*b*) were liquid and were therefore examined in dilute hydrochloric acid solution without isolation. Approximate concentrations of the deliquescent hydrochlorides were determined subsequently by evaporation. The azepine hydrochlorides had $[\alpha]_{5461}^{18\cdot5}$ +45° and $[\alpha]_{5461}^{18\cdot5}$ −41·5° respectively. They racemised in aqueous hydrochloric acid solution with a half-life of 6·5 hr. at 80° and of 2·0 hr. at 91°. At lower temperatures the rate was too slow for convenient measurement; at higher temperatures the solvent was too near its boiling point. These rates give a value of about 28 kcal. mole^{-1} for the activation energy but the data are inadequate for accurate assessment of *E*. It is, however, clear that the compound is much more optically stable than the hydrocarbon ester (V), which was inactive after 5 hr. at 32·5°.[3] Slight racemisation (perhaps a few units per cent.) probably occurred during the Hofmann degradation.

The quaternary ephedrinium iodide[1] without *ortho*-substituents (VII; R = H) was also re-examined. It showed no mutarotation in chloroform solution at temperatures in the range 0—50°.

Experimental

(In all polarimetric readings, unless otherwise stated, $l = 2$.)

2 : 2′-Bisbromomethyl-6 : 6′-dinitrodiphenyl.—2 : 2′-Dimethyl-6 : 6′-dinitrodiphenyl was prepared by the method of Carlin and Foltz,[13] except that it was found preferable to carry out the Ullmann reaction at 150° instead of 200°. The dinitroditolyl, m. p. 110·5—112° (10·7 g.), was heated under reflux in dry carbon tetrachloride (64 c.c.) with *N*-bromosuccinimide (14·3 g.) and benzoyl peroxide (0·1 g.) for 5 hr. A little more (0·05 g.) catalyst was washed in with carbon tetrachloride (20 c.c.) and heating continued for another 3 hr. The hot solution was filtered and concentrated; crude dibromide separated on cooling. Some of it had also crystallised with the succinimide and was isolated by washing out the latter with much cold water.

[10] Kleiderer and Adams, *J. Amer. Chem. Soc.*, 1931, **53**, 1575; 1933, **55**, 4219; Stanley, McMahon, and Adams, *ibid.*, p. 706; Stoughton and Adams, *ibid.*, 1932, **54**, 4426.
[11] Beaven and Hall, *J.*, 1956, 4637.
[12] Bell, *J.*, 1934, 835.
[13] Carlin and Foltz, *J. Amer. Chem. Soc.*, 1956, **78**, 1997.

The product was crystallised from dry benzene (yield, 9·5 g., 64%).* Recrystallisation gave pure 2 : 2′-bisbromomethyl-6 : 6′-dinitrodiphenyl as pale yellow pointed prisms, m. p. 184—185° (Found: C, 39·3; H, 2·1; N, 6·2; Br, 37·4. Calc. for $C_{14}H_{10}O_4N_2Br_2$: C, 39·1; H, 2·3; N, 6·5; Br, 37·2%). The use of slightly impure dinitroditolyl greatly reduced the yield of brominated product.

2 : 7-*Dihydro*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium Iodide*.—Piperidine (3·74 g., 2·2 mols.) was added to a solution of the dinitro-dibromide (8·6 g., 1 mol.) in benzene at 50° and the mixture kept at this temperature for 3½ hr. The solution was then decanted from the gum, which was washed with warm benzene and triturated with cold water. The bromide crystallised from water as a pale cream solid, m. p. 302—303° (decomp.) (5·6 g., 65%). It darkened rapidly in light and was therefore converted into the *iodide*, which crystallised from water in deep yellow prisms, m. p. 306—308° (decomp.) (Found: C, 47·4; H, 3·9; N, 8·85; I, 26·8. $C_{19}H_{20}O_4N_3I$ requires C, 47·4; H, 4·2; N, 8·7; I, 26·4%).

(−)-2 : 7-*Dihydro*-1-(2-*hydroxy*-1-*methyl*-2-*phenylethyl*)-1-*methyl*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*dibenzazepinium Bromide*.—A solution of (−)-ephedrine hemihydrate (12 g., 2·3 mols.) in benzene was dried (Na_2SO_4) and added to a solution of 2 : 2′-bisbromomethyl-6 : 6′-dinitrodiphenyl (12·9 g., 1 mol.) in dry benzene at 50°. The mixture became cloudy; it was kept at *ca.* 50° for 35 hr., during which a gum gradually separated. The gum solidified on treatment with water; it was washed with warm benzene and then with cold water (crude yield, 10·3 g.) and crystallised repeatedly from absolute ethanol. The less soluble quaternary (−)-*bromide* (2·5 g.) was obtained as yellow needles, m. p. 248° (decomp.), $[\alpha]^{23}_{5461}$ −709°, $[\alpha]^{23}_{D}$ −544° (*c* 0·994 in MeCN, *l* = 1) (Found: C, 56·3; H, 4·6; N, 8·25; Br, 15·6. $C_{24}H_{24}O_5N_3Br$ requires C, 56·0; H, 4·7; N, 8·2; Br, 15·5%).

(+)-2 : 7-*Dihydro*-1-(2-*hydroxy*-1-*methyl*-2-*phenylethyl*)-1-*methyl*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*dibenzazepinium Bromide*.—After separation of most of the (−)-isomer, ethanol was removed from the mother-liquor and the impure quaternary (+)-bromide obtained as a gum. Three crystallisations from acetonitrile gave the (+)-*bromide* as yellow needles, m. p. 228° (decomp.), $[\alpha]^{18}_{5461}$ +689°, $[\alpha]^{18}_{D}$ +533° (*c* 0·273 in MeCN) (Found: C, 55·6; H, 4·8; N, 8·1; Br, 15·2%). The sparing solubility of this isomer in acetonitrile meant that only very dilute solutions could be examined polarimetrically.

(−)-2 : 7-*Dihydro*-1-*methyl*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*dibenzazepine*.—A solution of the (−)-bromide (1·3 g.) in ethanol was kept on a steam-bath and treated, during 1 hr., with an aqueous suspension of silver oxide. After filtration, ethanol, water and β-methylstyrene oxide were removed under reduced pressure, a short period of heating at 120° being necessary to ensure complete removal of the epoxide. The residue was dissolved in ether, and the (−)-*amine* extracted with dilute hydrochloric acid and precipitated with ammonia. It crystallised from benzene–light petroleum (b. p. 60—80°) in yellow needles (0·5 g.), m. p. 169—170°, $[\alpha]^{19}_{5461}$ −1343° ± 5°, $[\alpha]^{19}_{D}$ −1030° ± 5° (*c* 0·197 in C_6H_6) (Found: C, 60·4; H, 4·2; N, 13·8. $C_{15}H_{13}O_4N_3$ requires C, 60·2; H, 4·4; N, 14·05%).

(+)-2 : 7-*Dihydro*-1-*methyl*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*dibenzazepine*.—Similar treatment of the (+)-bromide (1·1 g.) gave the (+)-*amine* (0·4 g.), m. p. 169—170°, $[\alpha]^{19}_{5461}$ +1333° ± 2°, $[\alpha]^{19}_{D}$ +1024° ± 2° (*c* 0·454 in C_6H_6) (Found: C, 59·8; H, 4·8; N, 14·1%).

Racemisation of (+)- *and* (−)-2 : 7-*Dihydro*-1-*methyl*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*dibenzazepine*.—The (+)-amine (0·198 g.) in benzene solution (100 c.c.) with $\alpha^{18\cdot5}_{5461}$ +2·64° was sealed in 8 tubes and heated in a thermostat at 125°. Tubes were removed at intervals, then chilled, and rotations read at 18·5°. During 15·25 hr. the rotation fell to +1·36°; $k = 1{\cdot}2 \times 10^{-5}$ sec.$^{-1}$. Heating of the last tube was continued for a few days; the solution was then inactive. Similar experiments at 145° gave $k = 7{\cdot}4 \times 10^{-5}$ sec.$^{-1}$; $E = 30$ kcal. mole^{-1}; $A = 10^{11\cdot5}$ sec.$^{-1}$.

(−)-2 : 7-*Dihydro*-1 : 1-*dimethyl*-4′ : 1″-*dinitro*-3 : 4-5 : 6-*dibenzazepinium iodide*, prepared from the (−)-amine, crystallised from ethanol and had m. p. 252—254° (decomp.), $[\alpha]^{19}_{5461}$ −813° in acetone (*c* 0·089) (Found: C, 43·1; H, 3·7; N, 9·5; I, 29·0. $C_{16}H_{16}O_4N_3I$ requires C, 43·5; H, 3·7; N, 9·5; I, 28·8%). Racemisation of an acetone solution in sealed tubes at 145° gave $k = 4{\cdot}05 \times 10^{-5}$ sec.$^{-1}$.

2 : 2′-*Difluoro*-6 : 6′-*dimethyldiphenyl*.[13]—2 : 2′-Dimethyl-6 : 6′-dinitrodiphenyl was reduced[15]

* Newman, Rutkin, and Mislow [14] report that they also tried this method of preparation of the dibromide (cf. ref. 9) but only obtained a 10% yield.

[14] Newman, Rutkin, and Mislow, *J. Amer. Chem. Soc.*, 1958, **80**, 465.

[15] Kenner and Stubbings, *J.*, 1921, **119**, 593.

and the resulting diamine converted into the tetrazonium borofluoride. Thermal decomposition at 100°, followed by steam-distillation, gave 2 : 2′-difluoro-6 : 6′-dimethyldiphenyl in 37% yield * (from the borofluoride), m. p. 44—45° (from methanol).

(+)- *and* (−)-4′ : 1″-*Difluoro*-2 : 7-*dihydro*-1-(2-*hydroxy*-1-*methyl*-2-*phenylethyl*)-1-*methyl*-3 : 4-5 : 6-*dibenzazepinium Bromide*.—A solution of 2 : 2′-difluoro-6 : 6′-dimethyldiphenyl (10 g.) in carbon tetrachloride (32 c.c.) was heated under reflux with *N*-bromosuccinimide (16·5 g.) and benzoyl peroxide (0·1 g.) for 8 hr. (Contrary to Wenner's experience [8] we found that the use of larger amounts of catalyst, with consequent liberation of bromine, did not improve the yield.) The hot solution was filtered and solvent removed from the filtrate. The residual dibromo-compound was a gum and was dissolved in dry benzene and used without further purification. A solution of (−)-ephedrine hemihydrate (16·5 g., 2·2 mols.) in benzene (175 c.c.) was dried (Na_2SO_4) and added to the solution of the dibromo-compound at 50°; the mixture was kept at 50° for 10 hr. Needles and a gum separated. The needles (presumably ephedrine hydrobromide) dissolved in water; the gum solidified (10·5 g., 50%) and was repeatedly crystallised from ethanol. The less soluble quaternary *bromide* separated as fluffy needles, m. p. 233—234° (decomp.), $[\alpha]_{5461}^{18\cdot5}$ +50°, $[\alpha]_{D}^{18\cdot5}$ +37·5° (*c* 0·439 in EtOH) (Found: C, 62·2; H, 5·3; N, 3·5; Br, 17·2. $C_{24}H_{24}ONBrF_2$ requires C, 62·6; H, 5·25; N, 3·0; Br, 17·4%).

Dilution of the mother-liquor with water gave the more soluble quaternary *bromide* as hydrated cubes, m. p. 230—232° (decomp.), $[\alpha]_{5461}^{18\cdot5}$ −55°, $[\alpha]_{D}^{18\cdot5}$ −41° (*c* 0·509 in EtOH) (Found: C, 60·6; H, 5·5; N, 2·9; Br, 16·6. $C_{24}H_{24}ONBrF_2,H_2O$ requires C, 60·3; H, 5·5; N, 2·9; Br, 16·7%).

(+)- *and* (−)-4′ : 1″-*Difluoro*-2 : 7-*dihydro*-1-*methyl*-3 : 4-5 : 6-*dibenzazepine*.—The (+)-quaternary bromide (1 g.) was dissolved in ethanol and the warm solution treated with freshly prepared silver oxide during 45 min. After filtration the solution was kept at about 70° while ethanol, water, and the epoxide were removed under reduced pressure. The residue was dissolved in 10% hydrochloric acid, and the solution washed with ether until the washings were no longer optically active. The solution had $\alpha_{5461}^{19\cdot5}$ +0·79° and $[\alpha]_{5461}^{18\cdot5}$ +45° (*c* of hydrochloride determined by subsequent evaporation, 0·877).

Similar treatment of the (−)-quaternary bromide (1 g.) gave (−)-amine. Its solution in 10% hydrochloric acid had $\alpha_{5461}^{18\cdot5}$ −0·47° and $[\alpha]_{5461}^{18\cdot5}$ −41·5° (*c* of hydrochloride, 0·566).

The *methiodide* [made from the (±)-amine after racemisation] crystallised from ethanol in prisms, m. p. 253—254° (Found: I, 32·7. $C_{16}H_{16}NIF_2$ requires I, 32·8%).

Racemisation of (+)- *and* (−)-4′ : 1″-*difluoro*-2 : 7-*dihydro*-1-*methyl*-3 : 4-5 : 6-*dibenzazepine*.—The solutions in 10% hydrochloric acid obtained from the Hofmann degradation were observed in a jacketed polarimeter tube round which water from a thermostat was circulating. At 80° $k = 2{\cdot}95 \times 10^{-5}$ sec.$^{-1}$; at 91° $k = 9{\cdot}75 \times 10^{-5}$ sec.$^{-1}$; whence $E = 27{\cdot}8$ kcal. mole^{-1} and $A = 10^{12{\cdot}7}$ sec.$^{-1}$.

4′ : 1″-*Difluoro*-2 : 7-*dihydro*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium Iodide*.—2 : 2′-Difluoro-6 : 6′-dimethyldiphenyl (4·36 g.) was brominated and the resulting dibromide treated in benzene solution with piperidine. The piperdinium bromide formed was very soluble in water and was converted into the less soluble *iodide*, which crystallised from water in needles (5·2 g., 60%), m. p. 268—270° (decomp.) (Found: C, 53·3; H, 4·3; N, 3·0; I, 29·35. $C_{19}H_{20}NIF_2$ requires C, 53·4; H, 4·7; N, 3·3; I, 29·7%).

We thank Imperial Chemical Industries Limited for a grant and the University of Aligarh for study leave (to S. A.).

Bedford College, University of London. [*Received, April 8th*, 1958.]

* No other recognisable product was isolated. However an attempt to convert 2-amino-2′-methyldiphenyl into the corresponding fluoro-compound failed and gave fluorene as the only product (cf. Mascarelli and Gatti [16]).

[16] Mascarelli and Gatti, *Atti IV Congr. naz. Chim. pura applicata*, 1933, 503.

619 *Steroids and Walden Inversion Part XL.* The Configurations of the Bromination Products of Androstan-17-one.*

By C. W. Shoppee, R. H. Jenkins, and G. H. R. Summers.

Bromination of androstan-17-one affords the 16α-bromo- and the 16 : 16-dibromo-ketone. With lithium aluminium hydride the former product gives the 16α-bromo-17β-hydrin whose reactions with chromium trioxide, zinc, and potassium hydroxide (giving unexpectedly androstan-17-one) are reported; use of sodium borohydride gives the 16α-bromo-17α- and -17β-hydrin, whose reactions (as above) are also reported.

16β-Bromoandrostan-17-one is obtained by two methods and its equilibration with the 16α-bromo-ketone by hydrogen bromide is investigated.

Structures and configurations are rigidly proved.

The results differ from Fajkos's experiences with 3β-methoxy- and 3β-acetoxy-5α-androstan-17-one probably owing to long-range effects ascribed to conformational transmission.

The ultraviolet and infrared spectra of the bromo-ketones and bromohydrins are discussed in relation to the geometry of the steroid ring D.

There are two general methods for determination of the configuration at the halogen-substituted position in α-bromo*cyclo*hexanones. The chemical method depends upon reduction with lithium aluminium hydride or sodium borohydride to epimeric bromohydrins; with alkali *trans*-bromohydrins yield epoxides, and *cis*-bromohydrins regenerate the original ketones, whilst catalytic reduction furnishes the epimeric alcohols of established configurations.[1,2] The physical method depends on the circumstance that the frequency of the spectral absorption maximum of the carbonyl group in an α-bromo*cyclo*hexanone is a function of θ, the angle between the C–Br dipole and the trigonal $>C^{+}-O^{-}$ bond projected on a plane perpendicular to the bond joining C–Br and $C^{+}-O^{-}$.[3,4] Thus, in the ultraviolet region, axial α-bromo*cyclo*hexanones (θ ~105°) show displacements of the wavelength ($\Delta\lambda$ +28 mμ) and intensity ($\Delta \log \varepsilon$ + 0·6) of the carbonyl absorption maximum, whereas the equatorial epimerides (θ ~ −15°) exhibit only small differences ($\Delta\lambda$ −5 mμ; $\Delta \log \varepsilon$ 0 to +0·3) with respect to the parent ketones;[4] conversely, in the infrared region, equatorial α-bromo*cyclo*hexanones exhibit an increase in the carbonyl frequency ($\Delta\nu_{max.}$ + 15—20 cm.$^{-1}$), whereas the axial epimerides show little, if any, displacement.[3,5]

Equatorial bromine in α-bromo*cyclo*hexanols [θ 60°] gives one or more intense absorption bands in the 700 cm.$^{-1}$ region, whilst axial bromine [θ 60° or 180°] gives one or more intense bands in the 500—600 cm.$^{-1}$ region;[6] whilst these characteristic frequencies, which reflect the weight and configuration of the bromine atom, are largely independent of the α-hydroxyl group (whether axial or equatorial), α-bromo*cyclo*hexanols with *trans*(di-equatorial)- or *cis*(axial-equatorial or equatorial-axial)-geometry, show considerable perturbation of the O–H and C–OH stretching frequencies ($\Delta\nu_{O-H}$: −25 to −48 cm.$^{-1}$; $\Delta\nu_{C-OH}$: +13 to +25 cm.$^{-1}$), the *trans*-diaxial isomerides show little or no perturbation ($\Delta\nu_{O-H}$: −3 to −7 cm.$^{-1}$; $\Delta\nu_{C-OH}$: +2 to +6 cm.$^{-1}$).[7] These last techniques permit determination of both the halogen and the hydroxyl configurations in α-bromo*cyclo*hexanols.

* Part XXXIX, *J.*, 1958, 1657.

[1] Fieser and Ettorre, *J. Amer. Chem. Soc.*, 1953, **75**, 700; Fieser and Dominguez, *ibid.*, p. 1704; Fieser and Huang, *ibid.*, p. 4837; cf. Corey, *ibid.*, p. 4832.

[2] James and Shoppee, *J.*, 1954, 4224; James, Rees, and Shoppee, *J.*, 1955, 1370; James and Shoppee, *J.*, 1956, 1064; Shoppee, Jenkins, and Summers, *J.*, 1958, 1657.

[3] R. N. Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.

[4] Cookson, *J.*, 1954, 282; Cookson and Dandegaonker, *J.*, 1955, 352.

[5] Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 2301, 3297; 1954, **76**, 175; 1955, **77**, 5415, 5418.

[6] Barton, Page, and Shoppee, *J.*, 1956, 331; Cummins and Page, *J.*, 1957, 3847; cf. Bellamy and Williams, *ibid.*, p. 4294.

[7] Nickon, *J. Amer. Chem. Soc.*, 1957, **79**, 243.

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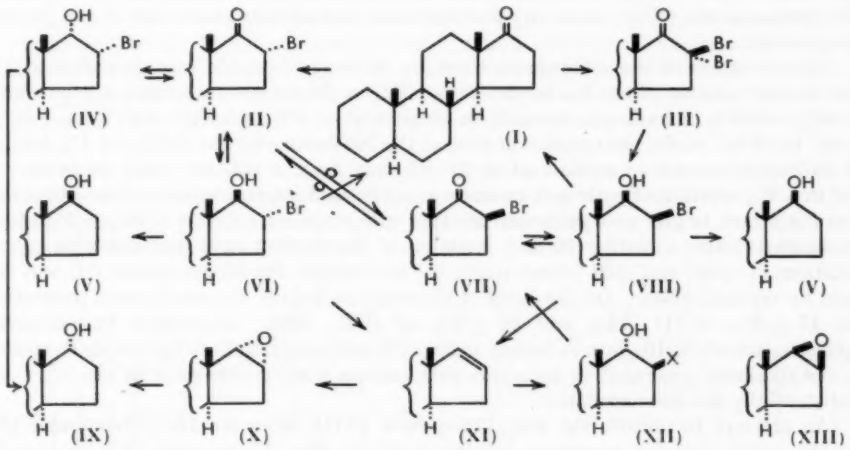
There is relatively little analogous chemical and physical information about α-bromo-*cyclo*pentanones and α-bromo*cyclo*pentanols. 15-, 16-, and 17-Keto-14α-steroids involve *cyclo*pentanone rings of fixed conformation; it seemed therefore of interest to investigate their bromination products, to ascertain the configurations of the α-bromo-ketones and those of the derived bromohydrins by chemical means, and to examine their spectral characteristics in the infrared and the ultraviolet region with a view to correlation with the geometry of ring D. The present paper deals with androstan-17-one and its derivatives.

Monobromination of androstan-17-one [8, 9, 10] (I) in acetic acid at 15° and purification of the product by crystallisation gave 75% of the 16α-bromo-ketone (II), whilst dibromination in ether–acetic acid at 36° gave the 16 : 16-dibromo-ketone (III).

The 16α-bromo-ketone (II) with lithium aluminium hydride in ether at 0° gave a 70% yield of the 16α-bromo-17β-hydrin (VI), m. p. 94°, $[\alpha]_D$ +2° (acetate, m. p. 142°, $[\alpha]_D$ −31°), oxidised by chromium trioxide in acetic acid at 20° to the 16α-bromo-ketone (II), and reductively debrominated with hydrogen and palladium in methanol to androstan-17β-ol [11, 12, 13] (V). Dehydrobromination with boiling methanolic potassium hydroxide



yielded, not the expected 16β : 17β-epoxide (XIII), but 86% of androstan-17-one (I), whose identity was confirmed by infrared spectroscopy, accompanied by 3% of androstan-17β-ol (V), possibly formed by reduction of the ketone (I) by methanol in the presence of methoxide ions.[14] The 16α-bromo-ketone (II) with sodium borohydride in methanol at 20° gave, after chromatography, the 16α-bromo-17α-hydrin (IV), m. p. 128°, $[\alpha]_D$ −5° (acetate, m. p. 200°, $[\alpha]_D$ −8°), and the 16α-bromo-17β-hydrin (VI), m. p. 90—94°, $[\alpha]_D$ +3°, giving an infrared spectrum identical with that of the material described above; the 16α-bromo-17α-hydrin (IV) with chromium trioxide in acetic acid at 20° gave the 16α-bromo-ketone (II), with hydrogen and palladium in methanol gave androstan-17α-ol [12, 13] (IX), and with hot methanolic potassium hydroxide gave androstan-17-one (I). In two experiments in which the sodium borohydride reduction product was isolated by direct crystallisation a compound of m. p. 147°, $[\alpha]_D$ −4°, was obtained; this gave correct

[8] Butenandt and Dannenbaum, *Z. physiol. Chem.*, 1934, **229**, 192.
[9] Fernholz and Chakravorty, *Ber.*, 1935, **68**, 353.
[10] Rosenkranz, Kaufmann, and Romo, *J. Amer. Chem. Soc.*, 1949, **71**, 3689.
[11] Marker, *ibid.*, 1940, **62**, 2543.
[12] Miescher and Kagi, *Helv. Chim. Acta*, 1939, **22**, 683.
[13] Shoppee, *Chem. and Ind.*, 1950, 454.
[14] Elks and Phillipps, *J.*, 1956, 4320.

XUM

analytical figures and appears to be a polymorph of the 16α-bromo-17α-hydrin (IV) (since in a third experiment fractions were obtained melting over the range 128—144°), or a molecular compound of the 17-epimeric bromohydrins (IV) and (VI).

The 16 : 16-dibromo-ketone (III) with sodium borohydride in methanol at 15° gave the 16β-bromo-17β-hydrin (VIII), m. p. 123°, $[\alpha]_D$ +3°, as sole product; its structure follows from its conversion by hydrogen and palladium into androstan-17β-ol (V), and by potassium hydroxide in methanol into androstan-17-one (I). The 16β-bromo-17β-hydrin (VIII) with chromium trioxide in acetic acid at 15° gave the 16β-bromo-ketone (VII), reconverted by reduction with sodium borohydride into the 16β-bromo-17β-hydrin (VIII).

The 16β-bromo-ketone was also obtained in another way. The three epimeric bromohydrins (IV), (VI), and (VIII) on brief treatment with zinc in acetic acid reacted with apparently equal facility, probably by the unimolecular elimination mechanism *E*1c*B*,[15] to afford androst-16-ene [16, 17] (XI). This hydrocarbon with perbenzoic acid gave the 16α : 17α-epoxide (X), reduced by lithium aluminium hydride to androstan-17α-ol (IX), and converted by hydrogen bromide in acetic acid into the 16β-bromo-17α-hydrin (XII; X = Br), m. p. 126°, $[\alpha]_D$ −4°, which with chromium trioxide in acetic acid at 15° gave the 16β-bromo-ketone (VII), whose infrared spectrum was identical with that of the previous preparation.

Epimerisation of the 16-bromo-ketones by hydrogen bromide was very slow at 15°; the specific rotation of the 16α-bromo-ketone (II) in chloroform containing a few drops of a 40% solution of hydrogen bromide in acetic acid at 20° increased only from +58° to +62° in 15 hr., whilst the specific rotation of the 16β-bromo-ketone (VII) in a 4% solution of hydrogen bromide in acetic acid at 20° fell only from +124° to +115° in 24 hr. At 55° in a 4% solution of hydrogen bromide in acetic acid interconversion of the epimerides was fairly fast, to give an equilibrium mixture with a specific rotation of 93° ± 2° in 6 hr., unchanged during a further 90 hr.; isolation of the product gave material with specific rotations of +95° and +91°, from which the less soluble 16α-bromo-ketone (II) was isolated by crystallisation. On the basis of the rotation values, the equilibrium proportions are 47 ± 3% of (II; 16α) and 53 ± 3% of (VII; 16β). Attempted base-catalysed epimerisation of the 16α-bromo-ketone at 20° with methanolic sodium hydroxide equivalent to the alkalinity generated in reduction with sodium borohydride gave an oil, $[\alpha]_D$ +10°, substantially free from bromine.

An attempt to prepare the 16β : 17β-epoxide (XIII) from the 16α : 17α-epoxide (XI) by the usual inversion procedure [acetolysis of the 16α : 17α-epoxide (XI) to give the 16β : 17α-diol 16-mono-acetate (XII: X = OAc), and treatment of this as the 17-toluene-*p*-sulphonate with potassium hydroxide] had to be abandoned for lack of material.

When the foregoing work was almost complete, there appeared a paper by Fajkos [18] describing the epimeric 16-bromo-derivatives of 3β-methoxy- and 3β-acetoxy-androstan-17-one with results so strikingly different from our own as to compel repetition of our work, and to merit brief description of his results.

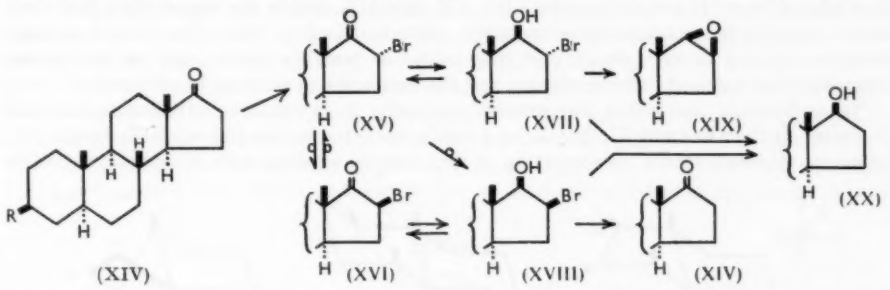
Bromination in acetic acid of 3β-methoxyandrostan-17-one (XIV; R = MeO) gave the 16α-bromo-ketone (XV; R = MeO) unaccompanied by the 16 : 16-dibromo-ketone. The 16α-bromo-ketone with lithium aluminium hydride in ether at 0° gave 45% of the 16α-bromo-17β-hydrin (XVII; R = MeO), which was oxidised by chromium trioxide in acetic acid at 20° to regenerate the parent 16α-bromo-ketone (XV; R = MeO), dehydrobrominated by potassium hydroxide to the 16β : 17β-epoxide (XIX; R = MeO), and debrominated by palladium in hydrogen to 3β-methoxyandrostan-17β-ol (XX; R = MeO). The 16α-bromo-ketone (XV; R = MeO) however, with sodium borohydride in methanol at 20°, gave 70% of the 16β-bromo-17β-hydrin (XVIII; R = MeO), converted by palladium

[15] James, Rees, and Shoppee, *J.*, 1955, 1370.
[16] Prelog, Ruzicka, and Wieland, *Helv. Chim. Acta*, 1944, **27**, 66.
[17] Miescher and Kagi, *ibid.*, 1949, **32**, 761, 764, 766.
[18] Fajkos, *Coll. Czech. Chem. Comm.*, 1955, **20**, 312.

XUM

and hydrogen into the 17β-ol (XX; R = MeO), by potassium hydroxide into the 3β-methoxy-ketone (XIV; R = MeO), and by chromium trioxide in acetic acid at 20° into the 16β-bromo-ketone (XVI; R = MeO). This 16β-bromo-ketone was isolated in small quantity by systematic fractional crystallisation of the crude product of the original bromination (being probably formed as the result of hydrogen bromide-catalysed epimerisation of the 16α-bromo-ketone); it was also obtained from the 16α-bromo-ketone by base-catalysed epimerisation at 20°, the equilibrium mixture of the epimeric bromo-3β-methoxy-ketones being estimated on the basis of its specific rotation as 20% of 16α- and 80% of 16β-isomer. It was suggested that reduction of the 16α-bromo-ketone (XV; R = MeO) with sodium borohydride in methanol, as opposed to lithium aluminium hydride in ether at 0°, is preceded by base-catalysed epimerisation at 20°, to give the 16β-bromo-ketone (XVI; R = MeO), which in fact affords 73% of the 16β-bromo-17β-hydrin (XVIII; R = MeO) when reduced with sodium borohydride in methanol.

Bromination of 3β-acetoxyandrostan-17-one (XIV; R = AcO) in acetic acid was much slower and yielded only a small amount of the 16α-bromo-ketone (XV; R = AcO), but in ethanol gave some 30% of the 16α-bromo-ketone accompanied by the 16 : 16-dibromo-ketone. The 16α-bromo-ketone was readily prepared by the action of bromine on the enolic acetate 3β : 17-diacetoxyandrost-16-ene, and afforded 17-epimeric 16α-bromohydrins (XVII and its 17α-epimeride; R = AcO) by reduction with lithium aluminium hydride or with lithium borohydride in ether at 0°, but yielded 60% of the 16β-bromo-17β-hydrin (XVIII; R = AcO) with sodium borohydride in methanol or with lithium borohydride in ethanol at 20°. Oxidation of the 16β-bromo-17β-hydrin (XVIII; R = AcO) with chromium trioxide in acetic acid furnished the 16β-bromo-ketone (XVI; R = AcO), which was prepared independently by Šorm and Fajkos [19] from 3β-acetoxy-16α : 17α-epoxyandrostane by fission with hydrogen bromide and oxidation of the resulting non-crystalline 16β-bromo-17α-hydrin with chromium trioxide. Finally, the 16α-bromo-



ketone (XV; R = AcO) was partly converted into the 16β-bromo-ketone (XVI; R = AcO) by treatment with hydrogen bromide, the equilibrium mixture being estimated on the basis of specific rotation to contain the epimerides in the proportion 16α 60% : 16β 40%.

The chemical evidence for the configurations of the various 16-bromoandrostan-17-ones prepared by us and by Fajkos appears unambiguous. It is supported by the available physical evidence. The molecular rotation data for the various androstan-17-ones and their 16-bromo-derivatives, and for the androstan-17-ols and their 16-bromo-derivatives are collected in Table 1.

It will be seen that, in terms of the configurations assigned, inversion of configuration of a 16-bromo-substituent (16α ⟶ 16β) leads consistently to increased dextrorotation; this is also true for 16-bromo-17α-hydrins (16α : −18°; 16β : −14°). The molecular-rotation data thus support the chemical evidence of configuration. The larger increments observed for the bromo-ketones than for the bromohydrins reflect the larger rotatory contribution of the 17-keto-group (+93°) than of the 17β-hydroxyl group (+11°). In

[19] Šorm and Fajkos, *Coll. Czech. Chem. Comm.*, 1955, **20**, 1478.

the bromo-ketones, the rotatory contribution of a 16α-bromine atom is negative, but that for a 16β-bromine atom is positive; in the bromohydrins, the rotational contribution of a 16α-bromine atom is again negative, whereas that for a 16β-bromine atom is also negative but less. In this connexion it may be recalled that the rotatory contributions for epimeric

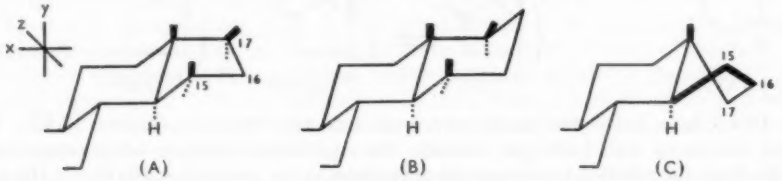
TABLE 1.

3β-Substituent R	Compound	$[\alpha]_D$	$[M]_D$	Δ16β–16α	ΔBr 16α	ΔBr 16β
H	Androstane	+2°	+5°	—	—	—
	17-Ketone (I)	+98	+268	—	—	—
	16α-Bromo-ketone (II)	+58	+204	+234°	−64°	—
	16β-Bromo-ketone (VI)	+124	+438		—	+170°
	16 : 16-Dibromo-ketone (III)	+62	+268	—	−170	+64
MeO	17-Ketone (XIV)	+79	+240	—	—	—
	16α-Bromo-ketone (XV)	+45	+174	+232	−66	—
	16β-Bromo-ketone (XVI)	+106	+406		—	+166
AcO	17-Ketone (XIV)	+69	+229	—	—	—
	16α-Bromo-ketone (XV)	+38	+154	+232	−75	—
	16β-Bromo-ketone (XVI)	+94	+386		—	+157
	16 : 16-Dibromo-ketone	+45	+223		−163	+69
H	17β-Alcohol (V)	+13	+36	—	—	—
	16α-Bromo-17β-hydrin (VI)	+2	+7	+5	−29	—
	16β-Bromo-17β-hydrin (VIII)	+3·5	+12		—	−24
MeO	17β-Alcohol (XX)	+15	+46	—	—	—
	16α-Bromo-17β-hydrin (XVII)	−8	−31	+16	−77	—
	16β-Bromo-17β-hydrin (XVIII)	−4	−15		—	−61

16-hydroxyl groups are both negative: ΔOH-16α −36°, ΔOH-16β −20°, and it can be shown [20] that ΔOH and ΔHal values tend, in the absence of vicinal action, to be similar in both sign and magnitude at the various nuclear positions.

We have also investigated the ultraviolet and the infrared spectral characteristics of androstan-17-one (I) and its bromides (II, VII, and III), less in the expectation that they would support the configurations assigned, than in the hope that they would provide evidence relating to the geometry of ring D and so possibly throw light on the factors controlling the rates of interconversion and the equilibria of pairs of 16-epimerides.

In androstane and other 14α-steroids generally, it is usual to attribute equatorial character to the 15α- and 17β-bonds, and axial character to the 15β- and 17α-bonds (A), either by reference to the conformation of ring C or by analogy with the conformation of



the terminal ring of D-homoandrostane (B). This approximation cannot be applied to the bonds attached to $C_{(16)}$. Spectroscopic measurements [21] and entropy calculations [22,23] indicate that the 5-carbon ring of *cyclo*pentane is puckered as the result of 1 : 2-repulsions between adjacent C–H bonds. The decrease in stability caused by the deformation of the tetrahedral angles is more than compensated by the gain in stability resulting from reduction of the repulsive forces between adjacent C–H bonds by staggering; C_2 symmetry with $C_{(3)}$ lying below and $C_{(5)}$ above a plane containing $C_{(1)}$, $C_{(2)}$, and $C_{(4)}$ has been confirmed by determination of the molar Kerr constants for *cyclo*pentane and the

[20] Shoppee, Howden, and Lack, unpublished work.
[21] Tschamler and Voetter, *Monatsh.*, 1952, **83**, 302, 835, 1228.
[22] Aston, Schumann, Fink, and Doty, *J. Amer. Chem. Soc.*, 1941, **63**, 2039; 1943, **65**, 341.
[23] Kilpatrick, Pitzer, and Spitzer, *ibid.*, 1947, **69**, 2483.

*cyclo*pentyl halides by Le Fèvre and Le Fèvre.[24] The same arrangement is also adopted by *cyclo*pentanone,[24] and supporting evidence has been furnished by Brutcher *et al.*;[25] these workers confirmed the values of the carbonyl stretching frequency in the infrared spectrum found by Corey [5] for *cyclo*pentanone and the α-halogeno*cyclo*pentanones, and compared the frequency displacements with those observed for the planar structures present in indan-2-one and camphor and their α-halogeno-derivatives. Table 2 gives the infrared spectral data, together with the positions of the ultraviolet carbonyl absorption band determined by Kumler and Huitric [25] or recorded by Cookson.[4]

TABLE 2.

	$\nu_{max.}$ (in CCl_4) (cm.$^{-1}$)	$\Delta\nu$	$\lambda_{max.}$ (mμ)	$\Delta\lambda$	log ε	Δ log ε	θ
*cyclo*Pentanone	1742	—	287	—	—	—	—
α-Chloro*cyclo*pentanone	1755	+13	302	+15	—	—	~80°
α-Bromo*cyclo*pentanone	1750	+8	311	+24	—	—	~80
Indan-2-one	1753	—	—	—	—	—	—
1-Chloroindan-2-one	1772	+19	—	—	—	—	60
1-Bromoindan-2-one	1766	+13	—	—	—	—	60
Camphor	1744	—	288	—	1·45	—	—
3-*exo*-Chlorocamphor	1762	+18	306	+18	1·72	0·27	~55
3-*endo*-Chlorocamphor	1763	+19	305	+17	1·75	0·3	~65
3-*exo*-Bromocamphor	1760	+16	312	+24	1·95	0·5	~55
3-*endo*-Bromocamphor	1758	+14	310	+22	1·95	0·5	~65
3 : 3-Dichlorocamphor	1774	+30	310	+22	1·82	0·37	—
3 : 3-Dibromocamphor	1766	+22	323	+35	1·88	0·43	—

The increments $\Delta\nu$ are smaller and the differences $\Delta\lambda$ are larger for the *cyclo*pentanones than for the indan-2-ones and camphors; it is therefore concluded that the projected angle between the C–Hal dipole and the $^{\delta}C{-}O^{-}$ dipole in the former must be greater than 60°; in fact, the Le Fèvre model for *cyclo*pentanone requires an angle of ~78°.

The steroid ring D is a *cyclo*pentane ring of fixed conformation, in which adoption of the puckered C_2 symmetry of *cyclo*pentane is compelled by the *trans*-C/D-ring fusion. Departures from the tetrahedral angle resulting from the ring-fusion and from the introduction of trigonal carbon and other substituents are difficult to estimate, but if the 13β-methyl group and the 14α-hydrogen atom constitute the vertical, then $C_{(13)}$, $C_{(14)}$, and $C_{(16)}$ lie in a plane which makes an angle of 19° 28′ to the horizontal (C). The 16α-C–H and 16β-C–H bonds are symmetrically disposed (*a*) at an angle $\alpha = \sim 55°$ to the plane defined by $C_{(15)}$, $C_{(16)}$, and $C_{(17)}$, and (*b*) at an angle $\beta = \sim 39°$ to the vertical in the plane *z* at right

TABLE 3.

	$\nu_{max.}$ (in CCl_4) (cm.$^{-1}$)	$\Delta\nu$ (cm.$^{-1}$)	$\lambda_{max.}$ (mμ)	$\Delta\lambda$ (mμ)	log ε	Δ log ε
Androstan-17-one (I)	1746	—	292	—	1·72	—
16α-Bromoandrostan-17-one (II)	1752 [a] 1754	+7	314	+22	2·01	0·29
16β-Bromoandrostan-17-one (VII)	1754 [a]	+8	312	+20	1·90	0·18
16 : 16-Dibromoandrostan-17-one (III)	1754 1763	+17	320	+28	1·91	0·19

[a] Independent measurements, which also gave $\nu_{max.}$ 1751 cm.$^{-1}$ for (II) and 1754 cm.$^{-1}$ for (VII) (both in CS_2).

angles to the general plane *x* of the ring-system [given by $\cos\beta = \cos(90° - \alpha) . \cos 19° 28'$]. The infrared and the ultraviolet spectral characteristics for androstan-17-one (I) and its 16-bromo-derivatives (II, VII, III) are set out in Table 3.

It will be seen that the increments $\Delta\nu$ and $\Delta\lambda$ are approximately equal for both the

[24] Le Fèvre and Le Fèvre, *J.*, 1956, 3549.
[25] Brutcher, Roberts, Barr, and Pearson, *J. Amer. Chem. Soc.*, 1956, **78**, 1507; cf. Kumler and Huitric, *ibid.*, p. 3369.

XUM

epimeric 16-bromo-ketones, and correspond in magnitude with those found for α-bromo-*cyclo*pentanone. Fajkos[18] records $\nu_{max.}$ 1753 cm.$^{-1}$ for both 16α- and 16β-bromo-3β-methoxyandrostan-17-one (XV, XVI; R = MeO), but fails to state the solvent; his value for 3β-methoxyandrostan-17-one (XIV) is 1735 cm.$^{-1}$ (solvent unspecified). The interactions of the C–Br dipole and the $^{+}$C–O^{-} dipole are thus nearly the same, so that the C–Br bonds in both epimers make the same angle with the plane of $C_{(15)}$, $C_{(16)}$, and $C_{(17)}$. This confirms indirectly the validity of the Le Fèvre model for *cyclo*pentanone, which requires a symmetrical arrangement of the 16α-C–H and 16β-C–H bonds for *trans*-C/D-steroid 17-ketones.[26] The Le Fèvre model, however, predicts an unsymmetrical arrangement of the exocyclic bonds of $C_{(15)}$ and of $C_{(17)}$ in *trans*-C/D-steroid 16-ketones, and an experimental study is in progress. For αα-dibromo*cyclo*hexanones, in the ultraviolet region, the equatorial bromine atom reduces by about one half the increment contributed by the axial bromine atom to the position of $\lambda_{max.}$ ($\Delta\lambda$*gem.*-Br_2 + 12 to + 15 mμ),[4] and conversely, in the infrared region the axial bromine atom has little effect on the increase in the carbonyl stretching frequency contributed by the equatorial bromine atom ($\Delta\nu$*gem.*-Br_2 + 17 cm.$^{-1}$);[3] the αα-dibromo*cyclo*pentanone (III) shows $\Delta\lambda$ +28 mμ and $\Delta\nu$ +17 cm.$^{-1}$, and, like 3 : 3-dibromocamphor (see Table 2), does not appear to conform to the homologous pattern.

The principal differences exhibited by our work (3β-substituent = H) and that of Fajkos[18] (3β-OMe, -OAc) are the variation with the nature of the 3β-substituent (i) of the rate of epimerisation of the 16α-bromo-17-ketones as disclosed by the occurrence of retention, as opposed to inversion of configuration at $C_{(16)}$, on reduction with sodium borohydride in methanol at 20°, (ii) of the position of equilibrium amongst the three pairs of epimeric 16-bromo-17-ketones, and (iii) of the production of 16β : 17β-epoxides.

If the inversion at $C_{(16)}$ reported by Fajkos is due to base-catalysed epimerisation of the 16α-bromo-ketones (XV) before reduction, the rate of enolisation must be rapid by comparison with the rate of reduction, for otherwise the process should lead to mixtures of 16-epimeric bromohydrins. Even so, it is not clear why inversion at $C_{(16)}$ is not also observed in the sodium borohydride reductions of the 16β-bromo-ketones (XVI), especially in the case of the 3β-acetoxy-compound (XVI; R = AcO) which at equilibrium is converted to the extent of 60% into the 16α-bromo-epimeride (XV; R = AcO).

In studies of 16-substituted steroids Šorm *et al.* have shown that the thermodynamic stabilities of pairs of epimerides vary from case to case: 16β-OH > 16α-OH;[27,28] 16α-CO_2H > 16β-CO_2H;[29] 16α-COMe > 16β-COMe;[30] and have suggested that the variation depends on the nature of the 16-substituent. It now appears that the nature of the 3-substituent is also a factor in the situation and influences both reaction rates and equilibria at $C_{(16)}$:

3β-Substituent R	Rate of epimerisation of 16α-bromo-ketones: (OH^- at ~20°)	Position of equilibrium 16α : 16β of 16-bromo-ketones (H^+ at ~20°)
H	Slow	47 : 53
MeO	Fast	20 : 80
AcO	Fast	60 : 40

These qualitative or semiquantitative variations in the properties of compounds with identical structures (apart from the 3β-substituent) are inexplicable in terms of 1 : 3-interactions, *e.g.*, 13β-Me/16β-Br and 14α-H/16α-Br, and suggest the operation of influences transmitted across a rigid, saturated, and conformationally unambiguous structure from $C_{(3)}$ in ring A to $C_{(16)}$ in ring D—a distance of about 9 Å. They appear to constitute a

[26] R. N. Jones and Roberts, *Chem. and Ind.*, 1957, 1269.
[27] Fajkos and Šorm, *Coll. Czech. Chem. Comm.*, 1954, **19**, 349; 1955, **20**, 1464.
[28] Šorm and Hovak, *ibid.*, 1956, **21**, 926.
[29] Fajkos and Šorm, *ibid.*, 1954, **19**, 766.
[30] Fajkos and Šorm, *Chem. Listy*, 1956, **50**, 791.

further example of the long-range effects in saturated alicyclic systems ascribed to conformational transmission.[31]

We reserve comment on the formation of androstan-17-one (I) from the *trans*-bromohydrin (VI) in contrast to the production of 16β : 17β-epoxides (XIX; R = MeO, AcO) from the *trans*-bromohydrins (XVI; R = MeO, AcO), because various mechanistic possibilities are available which cannot at present be distinguished. *trans*-Geometry may be essential for mechanisms involving synchronous covalency changes, *e.g.*, " internal " S_N2, *E2*, but not for stepwise mechanisms, *e.g.*, S_N1 (*E1*) and *E1cB*, in the course of which the original geometry disappears.

Experimental

For general experimental directions see *J.*, 1958, 1657. $[\alpha]_D$ are in $CHCl_3$; $\lambda_{max.}$ were determined for EtOH solutions on a Unicam S.P. 500 spectrometer with corrected scale, and $\nu_{max.}$ for CCl_4 solutions on a Grubb-Parsons double-beam grating instrument. Unless otherwise specified, alumina was of Spence Type II (activity ~II).

16α-*Bromoandrostan*-17-*one* (II).—Androstan-17-one (m. p. 120°; 710 mg.), dissolved in acetic acid (50 c.c.) and ether (20 c.c.), was treated with a 10% solution of bromine in acetic acid (5 c.c., 1·1 mol.), and 2 drops of a solution of hydrogen bromide in acetic acid were added. After being kept overnight at 15°, the colourless solution was worked up in the usual way to an oil, which crystallised on trituration with ether–methanol (m. p. 181—185°). Two recrystallisations from light petroleum (b. p. 60—80°) gave 16α-*bromoandrostan*-17-*one* (900 mg.), m. p. 197°, $[\alpha]_D$ +58° (*c* 1·2) [Found (after drying at 70°/0·01 mm. for 6 hr.): C, 64·7; H, 8·4. $C_{19}H_{29}OBr$ requires C, 64·6; H, 8·2%]. Other preparations had m. p. 193—197°, $[\alpha]_D$ +58° (*c* 1·08).

Lithium Aluminium Hydride Reduction of 16α-*Bromoandrostan*-17-*one*: 16α-*Bromoandrostan*-17β-*ol* (VI).—16α-Bromoandrostan-17-one (1·47 g.) in dry ether (150 c.c.) at 0° was treated with lithium aluminium hydride (600 mg.). After 2 hr., the excess of reagent was destroyed by addition of ice followed by 2N-sulphuric acid. The product, isolated in the usual way, was an oil, which crystallised on addition of light petroleum; it was chromatographed on aluminium oxide (40 g.; Woelm, acid) in light petroleum (b. p. 60—80°). Elution with light petroleum–benzene (1 : 4, 2 × 200 c.c.; and 1 : 2, 200 c.c.) gave fractions 1—3 as oils (49 mg.); elution with benzene (7 × 200 c.c.) gave fractions 4—10, which crystallised from light petroleum (m. p. 90—94°); use of ether–benzene (1 : 19, 3 × 200 c.c.) afforded fractions 11—14, which crystallised (m. p. 86—92°) from light petroleum. Fractions 4—14 were united (1005 mg.) and recrystallised several times from light petroleum, to give 16α-*bromoandrostan*-17β-*ol*, m. p. 92—94°, $[\alpha]_D$ +2° (*c* 0·8) [Found (after drying at 20°/0·02 mm. for 16 hr.): C, 64·0; H, 8·4. $C_{19}H_{31}OBr$ requires C, 64·2; H, 8·7%], $\nu_{max.}$ 3632 cm.$^{-1}$ (O–H stretching), which was converted by acetic anhydride–pyridine in 12 hr. at 20° into the *acetate*, m. p. 142—144°, $[\alpha]_D$ −31° (*c* 1·8) [Found (after drying at 20°/0·02 mm. for 16 hr.): C, 63·2; H, 8·2. $C_{21}H_{33}O_2Br$ requires C, 63·5; H, 8·3%]. Further elution with ether–benzene (1 : 19, 2 × 200 c.c.) gave fractions 15 and 16 (92 mg., 55 mg.) which did not crystallise, whilst use of ether–benzene and chloroform gave only traces of oil (10 mg., 8 mg.).

Reactions of the 16α-*Bromo*-17β-*hydrin* (VI).—(*a*) The bromohydrin (128 mg.) was oxidised with a 2% solution of chromium trioxide in acetic acid at 20°; after 1 hr., the crystalline product was filtered off, and the filtrate worked up in the usual way, to give 16α-bromoandrostan-17-one (120 mg.), m. p. and mixed m. p. 193—196°.

(*b*) The bromohydrin (120 mg.) in methanol (5 c.c.) was shaken with 5% palladium–charcoal (150 mg.) in hydrogen at 20° for 18 hr. The product, isolated in the usual manner, was androstan-17β-ol, m. p. and mixed m. p. 165°, $[\alpha]_D$ +11° (*c* 1·2), after two crystallisations from aqueous acetone; on admixture with androstan-17α-ol, the m. p. was depressed to ~128°. Alternatively, the bromohydrin (60 mg.) in methanol (5 c.c.) was shaken with platinum oxide (60 mg.) in hydrogen at 20° for 16 hr. Filtration and evaporation in a vacuum gave androstan-17β-ol (47 mg.), transition to needles at 138—139°, m. p. 164—165°, whose infrared spectrum was identical with that of a genuine specimen.

(*c*) The bromohydrin (830 mg.) was refluxed with potassium hydroxide (830 mg.) in methanol (83 c.c.) for 48 hr. After partial removal of methanol under reduced pressure, and addition of

[31] Barton and Head, *J.*, 1956, 932; Barton, Head, and May, *J.*, 1957, 935.

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water, the product was extracted with ether, washed with water, dried, and evaporated to an oil, which was chromatographed on aluminium oxide (30 g.; Woelm, neutral) in light petrolem. Elution with light petroleum (2 × 100 c.c.) yielded no eluates, but further use of light petroleum (100 c.c.) gave fraction 3, which crystallised (44 mg.). Elution with benzene–light petroleum (1 : 9, 4 × 100 c.c.) gave crystalline fractions 4—7 (382, 87, 16, and 11 mg.); use of benzene–light petroleum (1 : 4, 100 c.c.) gave a crystalline fraction 8, but use of benzene (100 c.c.) gave no eluate. Fractions 4 and 5 were combined and recrystallised to yield androstan-17-one, m. p. 120°, whose infrared spectrum was identical with that of an authentic specimen; fractions 3, 6, 7, and 8 also consisted of this ketone. Finally, elution of the column with ether (100 c.c.) furnished androstan-17β-ol (20 mg.), m. p. 161° (mixed m. p. 161—164°) after recrystallisation from light petroleum.

(*d*) The bromohydrin (130 mg.) was refluxed with zinc dust in ethanol (5 c.c.) for 3 hr.; the product, isolated in the normal manner, was chromatographed on aluminium oxide (4 g.) in pentane. Elution with pentane gave an oil (92 mg.), which crystallised from acetone to give androst-16-ene, m. p. and mixed m. p. 76—77°.

Sodium Borohydride Reduction of 16α-*Bromoandrostan*-17-*one*: 16α-*Bromoandrostan*-17α-*ol* (IV).—(*a*) 16α-Bromoandrostan-17-one (m. p. 193°; 340 mg.) in ether (25 c.c.) was treated with sodium borohydride (100 mg.) in methanol (12 c.c.) at 20° for 18 hr. After the usual working up, the product was chromatographed on aluminium oxide (8 g.; Woelm, neutral) in light petroleum. Elution with light petroleum (4 × 30 c.c.) gave an oil (140 mg.), which crystallised from acetone–methanol to give 16α-*bromoandrostan*-17α-*ol*, m. p. 125—128°, $[\alpha]_D$ −5° (*c* 1·0) [Found (after drying at 20°/0·02 mm. for 12 hr.): C, 64·1; H, 8·8. $C_{19}H_{31}OBr$ requires C, 64·2; H, 8·7%], and was converted by acetic anhydride–pyridine at 20° in 12 hr. into the *acetate*, m. p. 200—203°, $[\alpha]_D$ −5° (*c* 1·0) after two recrystallisations from acetone [Found (after drying at 50°/0·01 mm. for 12 hr.): C, 63·6; H, 8·4. $C_{21}H_{33}O_2Br$ requires C, 63·5; H, 8·3%]. Further elution of the column with benzene–light petroleum (1 : 1, 3 × 40 c.c.) gave an oil (130 mg.), which crystallised from light petroleum to give 16α-bromoandrostan-17β-ol, m. p. 90—94°, $[\alpha]_D$ +3° (*c* 1·25), whose infrared absorption spectrum was identical with that of the preparation, m. p. 92—94°, obtained by use of lithium aluminium hydride. A second experiment gave the same two products.

(*b*) 16α-Bromoandrostan-17-one (120 mg.) in ether (20 c.c.) was treated with sodium borohydride (40 mg.) in methanol (10 c.c.). After 18 hr. at 15°, the solution was diluted with water and extracted with ether. Working up furnished an oil, which crystallised readily from acetone to give either a polymorphic form of 16α-bromoandrostan-17α-ol, or more probably a molecular compound of the 16α-bromo-17-hydrins (IV, VI) (110 mg.), m. p. 144—147°, $[\alpha]_D$ −4° (*c* 1·5) [Found (after drying at 20°/0·01 mm. for 12 hr.): C, 64·0; H, 8·8. Calc. for $C_{19}H_{31}OBr$: C, 64·2; H, 8·7%]. In a second experiment, direct crystallisation of the product, from acetone, again gave the compound, m. p. 146—149°, but a third experiment gave a product of m. p. 128—141°.

Reactions of the 16α-*Bromo*-17α-*hydrin* (IV).—(*a*) The bromohydrin (m. p. 128°; 43 mg.) was oxidised with a 2% solution of chromium trioxide in acetic acid at 20° for 12 hr. The product, isolated in the usual way, gave a nearly quantitative yield of 16α-bromoandrostan-17-one, m. p. and mixed m. p. 191—193°, $[\alpha]_D$ +58° (*c* 1·1).

(*b*) The bromohydrin (m. p. 125—127°; 30 mg.) in methanol (5 c.c.) was shaken with 5% palladium–charcoal (50 mg.) in hydrogen at 20° for 40 hr. The product, isolated in the usual way, was androstan-17α-ol, m. p. and mixed m. p. 142—144° after recrystallisation from aqueous acetone.

(*c*) The bromohydrin (m. p. 125—127°; 40 mg.) was refluxed with potassium hydroxide (120 mg.) in methanol (15 c.c.) for 2·5 hr. After saturation with carbon dioxide, partial removal of methanol under reduced pressure, and dilution with water, the product was isolated in the usual way and crystallised from hexane to give androstan-17-one (30 mg.), m. p. and mixed m. p. 119—121°, $[\alpha]_D$ +94° (*c* 1·1).

(*d*) The bromohydrin (100 mg.) was refluxed with zinc dust (500 mg.) in acetic acid (15 c.c.) for 6 hr.; the warm solution was filtered, acetic acid largely removed at 10 mm., and the product extracted with ether. The usual procedure gave an oil, which was dissolved in pentane and filtered through a column of aluminium oxide (5 g.); the filtrate was evaporated and the product crystallised twice from acetone, to yield androst-16-ene, m. p. and mixed m. p. 74—76°.

16 : 16-*Dibromoandrostan*-17-*one* (III).—Androstan-17-one (2·0 g.), in ether (200 c.c.), was

refluxed with a 50% solution of bromine in acetic acid (5 c.c., 2·1 mol.) for 24 hr. Water was then added to the colourless solution, and the ethereal layer separated and worked up in the usual way. The resultant oil crystallised readily from ether to give in high yield **16 : 16-*dibromoandrostan*-17-*one***, m. p. 179°, $[\alpha]_D$ +62° (*c* 1·1) [Found (after drying at 50°/0·01 mm. for 7 hr.): C, 53·2; H, 6·7. $C_{19}H_{28}OBr_2$ requires C, 52·9; H, 6·5%]. A second preparation had m. p. 182°.

16β-*Bromoandrostan*-17β-*ol* (VIII).—**16 : 16**-Dibromoandrostan-17-one (220 mg.) in ether (40 c.c.) was treated with a solution of sodium borohydride (50 mg.) in methanol (20 c.c.) at 15° for 18 hr. The mixture was diluted with water and extracted with ether, and the product isolated in the usual way, to give **16β-*bromoandrostan*-17β-*ol*** (150 mg.), m. p. 123°, $[\alpha]_D$ +3·5° (*c* 1·7), after recrystallisation from acetone [Found (after drying at 40°/0·01 mm. for 18 hr.): C, 64·6; H, 8·9. $C_{19}H_{31}OBr$ requires C, 64·2; H, 8·7%]. A marked depression of m. p. was observed on admixture with the form of (IV), m. p. 128°, $[\alpha]_D$ −5°, and a second preparation gave material of m. p. 123—124°.

Reactions of the **16β-*Bromo*-17β-*hydrin*** (VIII).—(*a*) The bromohydrin (150 mg.) and 20% palladium–charcoal (120 mg.) in methanol (45 c.c.) were shaken in hydrogen at 20° for 4 hr. The product was isolated in the usual manner and chromatographed on a column of aluminium oxide (4·5 g.) prepared in pentane. Elution with pentane gave androstan-17-one (80 mg.), m. p. and mixed m. p. 118°, $[\alpha]_D$ +98° (*c* 1·1). Elution with benzene–pentane (1 : 1) and with benzene gave androstan-17β-ol, m. p. and mixed m. p. 161—163° (from light petroleum).

(*b*) The bromohydrin (340 mg.) was treated with potassium hydroxide (900 mg.) in methanol (35 c.c.) at 15° overnight. The solution was then refluxed for 3 hr., diluted with water, and worked up in the usual way, to give androstan-17-one (270 mg.), m. p. and mixed m. p. 119°.

(*c*) The bromohydrin (130 mg.) was refluxed with zinc dust (500 mg.) in acetic acid (40 c.c.) for 6 hr.; the warm solution was filtered, acetic acid removed at 10 mm., and the product isolated in the usual way as an oil (100 mg.), which crystallised from acetone to give androst-16-ene, m. p. and mixed m. p. 76—77°.

16β-*Bromoandrostan*-17-*one* (VII).—The 16β-bromo-17β-hydrin (493 mg.), dissolved in ether (2 c.c.) and acetic acid (10 c.c.), was oxidised with a 2% solution of chromium trioxide in acetic acid (10 c.c., 2 O) at 15° for 18 hr. Excess of chromium trioxide was destroyed by methanol, the solution diluted with water, and the precipitate filtered off, washed with water, and dried. Recrystal'isation from acetone gave **16β-*bromoandrostan*-17-*one*** (300 mg.), m. p. 128—129°, $[\alpha]_D$ +124° (*c* 1·4) [Found (after drying at 60°/0·01 mm. for 8 hr.): C, 64·6; H, 8·2. $C_{19}H_{29}OBr$ requires C, 64·6; H, 8·2%]. The m. p. was depressed on admixture with the starting material. A second oxidation gave material, m. p. 126°.

16β-*Bromoandrostan*-17β-*ol* (VIII).—To a solution of 16β-bromoandrostan-17-one (24 mg.) in ether (20 c.c.) was added a solution of sodium borohydride (30 mg.) in methanol (10 c.c.). After 18 hr. at 15° the mixture was diluted with water and extracted with ether, to afford, after the usual isolation procedure, 16β-bromoandrostan-17β-ol (15 mg.), m. p. and mixed m. p. 122—123°.

16α : 17α-*Epoxyandrostane* (X).—Androst-16-ene (200 mg.) in chloroform (4 c.c.) was treated with a chloroform solution of perbenzoic acid (1·2 mol.) at 0° for 3 days. The solution was diluted with water, extracted with ether, and worked up in the usual way to give an oil; this crystallised readily from ethanol, to afford **16α : 17α-*epoxyandrostane*** (150 mg.), m. p. 109—110°, $[\alpha]_D$ +1° (*c* 1·05) [Found (after drying at 50°/0·01 mm. for 12 hr.): C, 82·8; H, 11·0. $C_{19}H_{30}O$ requires C, 83·2; H, 10·9%].

16β-*Bromoandrostan*-17α-*ol* (XII).—The 16α : 17α-epoxide (120 mg.) in acetic acid (10 c.c.) was treated at 15° with a 5% solution of hydrogen bromide in acetic acid (2 c.c.) with stirring. After a few minutes a copious precipitate was formed. The mixture was diluted with a few drops of water, and the precipitate filtered off, washed with water, and dried. Crystallisation from acetone gave **16β-*bromoandrostan*-17α-*ol*** (110 mg.), m. p. 126—128°, $[\alpha]_D$ −4° (*c* 1·1) [Found (after drying at 50°/0·01 mm. for 8 hr.): C, 64·3; H, 8·8. $C_{19}H_{31}OBr$ requires C, 64·2; H, 8·7%]. The m. p. was depressed on admixture with 16β-bromoandrostan-17β-ol (VIII).

The 16β-bromo-17α-hydrin (99 mg.) in acetic acid (2 c.c.) was oxidised with a 2% solution of chromium trioxide in acetic acid (2 c.c.) at 15° overnight. Excess of the reagent was destroyed by methanol, the solution diluted, and the resultant precipitate filtered off, washed with water, dried, and crystallised from acetone to yield 16β-bromoandrostan-17-one, m. p. and mixed m. p. 128—129°, $[\alpha]_D$ +124° (*c* 1·25).

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Androstan-17α-ol (IX).—The 16α : 17α-epoxide (30 mg.) in ether (10 c.c.) was refluxed with lithium aluminium hydride (30 mg.) in ether (20 c.c.) for 6 hr. Excess of the reagent was decomposed with ice and 2N-sulphuric acid, and the product isolated in the usual way. The resulting oil was chromatographed on a column of aluminium oxide (1 g.) prepared in pentane. Elution with benzene–pentane (1 : 9) gave some starting material, m. p. 106—109°; elution with benzene yielded an oil, which crystallised from ethanol to give androstan-17α-ol, m. p. and mixed m. p. 142—146°, $[\alpha]_D$ −6° (*c* 0·8).

Interconversion of 16α- *and* 16β-*Bromoandrostan-17-one.*—(*a*) The 16α-bromo-ketone (II) (m. p. 197°, $[\alpha]_D$ +58°; 145 mg.) was dissolved in acetic acid (9 c.c.), 48% hydrobromic acid (1 c.c.) and a little chloroform (to give a homogeneous solution) were added, and the mixture was set aside at 25° for 4 days. Dilution with water and the usual ether-extraction gave a product (144 mg.), $[\alpha]_D$ +95° (*c* 1·1), which by crystallisation from ethanol gave the 16α-bromo-ketone, m. p. 191—193°. Fractional crystallisation of the mother-liquors gave the 16β-bromo-ketone, m. p. 118—122°, $[\alpha]_D$ +116° (*c* 0·5).

(*b*) The 16β-bromo-ketone (VII) (m. p. 124—126°, $[\alpha]_D$ +124°; 45 mg.) was dissolved in acetic acid (9 c.c.), and a 40% solution of hydrogen bromide in acetic acid (1 c.c.) added; at 20° after 24 hr. $[\alpha]_D$ was +115°. The mixture was kept at 55° for 6 hr., whereafter $[\alpha]_D$ was 91°; after being kept at 20° during a week-end, the product was isolated in the usual way and had $[\alpha]_D$ +91°, whilst crystallisation from ethanol gave the 16α-bromo-ketone, m. p. and mixed m. p. 191°.

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UNIVERSITY OF WALES, UNIVERSITY COLLEGE, SWANSEA.
DEPARTMENT OF ORGANIC CHEMISTRY, THE UNIVERSITY,
SYDNEY, NEW SOUTH WALES, AUSTRALIA. [*Received, February 5th,* 1958.]

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620. *The Reaction of 2-Keto-carboxylic Acids and Esters with Aromatic Compounds in Sulphuric Acid.**

By SAUL PATAI and SHELOMO DAYAGI.

Reactions of pyruvic acid, ethyl pyruvate, benzoylformic acid, ethyl benzoylformate, benzilic acid, and atrolactic acid with benzene, toluene, *o*-, *m*-, and *p*-xylene, *tert.*-butylbenzene and phenyl*cyclo*hexane in concentrated sulphuric acid at low temperatures have been studied.

The ketone-oxygen atom of the 2-keto-acids and -esters was exchanged in this reaction for two aryl groups and the hydroxyl group of the 2-hydroxy-acids for one aryl group. It is suggested that the reaction is an aromatic electrophilic substitution.

CONDENSATION of pyruvic acid with aromatic compounds in concentrated sulphuric acid was discovered by Bottinger [1,2] and further investigated by Bistrzycki *et al.*[3,4] They found that, depending on the reaction temperature, the product is either an αα-diarylpropionic acid or a 1 : 1-diarylethylene, which may be formed from the former by loss of water and carbon monoxide:

$$Me{\cdot}CO{\cdot}CO_2H + 2ArH \longrightarrow Me{\cdot}CAr_2{\cdot}CO_2H \longrightarrow Ar_2C{:}CH_2 + CO + H_2O$$

* Presented in outline at the 21st Meeting of the Israel Chemical Society, Jerusalem, 1957.

[1] Bottinger, *Ber.*, 1881, **14**, 1595.
[2] *Idem*, *Ber.*, 1883, **16**, 2071.
[3] Bistrzycki and Reintke, *Ber.*, 1905, **38**, 839.
[4] Bistrzycki and Mauron, *Ber.*, 1910, **43**, 2883.

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The reaction is useful for preparative purposes, and in some cases is the most convenient route to 1 : 1-diarylethylenes, *e.g.*, 1 : 1-di-*p*-tolylethylene.[3] Bistrzycki [4] found that phenylpyruvic acid reacts in a similar manner to pyruvic acid, although satisfactorily only with more active aromatic compounds. He also found [3] that of the three xylenes, *o*- and *m*-xylene react normally but *p*-xylene gives α-(2 : 5-dimethylphenyl)acrylic acid as the final product, *i.e.*, condensation takes place with only one molecule of *p*-xylene and is followed by dehydration. On the basis of further work we propose a mechanism for this reaction which we believe to be an electrophilic aromatic substitution.

Experimental

Reagents were purified commercial products or were prepared according to well-known procedures. M. p.s are corrected. Atrolactic acid (α-hydroxy-α-phenylpropionic acid) was prepared from pyruvic acid and an excess of phenylmagnesium bromide.[5] Pure concentrated sulphuric acid (*d* 1·83) was used.

Reaction of α-keto- and α-hydroxy-acids with aromatic hydrocarbons in concentrated sulphuric acid.

CO cpd. and wt. (g.)		H_2SO_4 (ml.)	ArH and amount		Temp.	Time (hr.)	Products	No.
$Ac{\cdot}CO_2H$	10	80	*o*-Xylene	26 g.	−10°	0·5	$(3:4\text{-}C_6H_3Me_2)_2CMe{\cdot}CO_2H$	1
,,	,,	,, [a]	*m*-Xylene	,,	,,	3	$(2:4\text{-}C_6H_3Me_2)_2CMe{\cdot}CO_2H$	2
,,	,,	,,	*p*-Xylene	,,	,,	0·5	$CH_2{:}C(2:5\text{-}C_6H_3Me_2){\cdot}CO_2H$	3
,,	,,	,,	$C_6H_5{\cdot}C_6H_{11}$ [b]	22 g.	−10° to −6°	1	$(p\text{-}C_6H_{11}{\cdot}C_6H_4)_2CMe{\cdot}CO_2H$	4
,,	,,	120	PhBu^t [b]	25 ml.	−10° to −5°	0·5	$CH_2{:}C(C_6H_4Bu^t\text{-}p)_2$	5
$Ac{\cdot}CO_2Et$	,,	80	Toluene	20 g.	−10° to −8°	1	$(p\text{-}C_6H_4Me)_2CMe{\cdot}CO_2Et$	6
							$CH_2{:}C(C_6H_4Me\text{-}p)_2$ [d]	7
							$CH_2{:}C(C_6H_4Me\text{-}p)_2$ [d]	8
$Bz{\cdot}CO_2Et$	,,	80	,,	15 g.	,,	1	$(p\text{-}C_6H_4Me)_2CPh{\cdot}CO_2Et$	9
							$p\text{-}C_6H_4Me)_2CPh{\cdot}CO_2H$ [e]	10
$Bz{\cdot}CO_2H$	5	,, [f]	,,	,,	10° to −5°	1	$(p\text{-}C_6H_4Me)_2CPh{\cdot}OH$	11
Benzilic acid	5	150 [f]	Benzene	30 ml.	−5° to −3° [d]	1·5	$CPh_2{\cdot}CO_2H$	12
			Toluene	,,	,,	1·5	$p\text{-}C_6H_4Me{\cdot}CPh_2{\cdot}OH$ [g]	13
Atrolactic acid	3·5	100	Benzene	,,	−12° to −8°	1	$p\text{-}C_6H_4Me{\cdot}CHPh{\cdot}CO_2H$	14

No.	M. p.	Yield (%)	Form (solvent)	Formula	Required (%) C	Required (%) H	Found (%) C	Found (%) H
1	146—147° [i]	30	—	—	—	—	—	—
2	169 [i]	28	—	—	—	—	—	—
3	128 [i]	20	—	—	—	—	—	—
4	246 [b]	25	Needles (dil. EtOH or AcOH)	$C_{27}H_{34}O_2$	83·1	8·7	83·2	9·2
5	103	26	Plates (acetone)	$C_{22}H_{28}$	90·4	9·6	90·3	9·4
6	Oil [c]	61	—	$C_{19}H_{22}O_2$	81·0	7·8	81·2	7·3
7	62 [i]	2	—	—	—	—	—	—
8	112	4	Needles (dil. EtOH)	$C_{23}H_{24}$	92·0	8·0	91·5	7·9
9	87·5	51	Needles (EtOH)	$C_{24}H_{24}O_2$	83·7	7·0	83·0	7·2
10	220	—	,,	$C_{23}H_{20}O_2$	83·5	6·4	83·5	6·7
11	80 [m]	68	,,	$C_{21}H_{20}O$ [k]	87·5	6·9	87·5	6·8
12	257 [n]	48	,,	—	—	—	—	—
13	74 [p]	58	Needles (ligroin)	$C_{26}H_{18}O$ [k]	87·6	6·6	87·2	6·9
14	138	44	Needles (dil. EtOH)	$C_{16}H_{16}O_3$	80·0	6·66	80·4	6·9

[a] 90% H_2SO_4. [b] Starts to sublime at 200—210°. [c] B. p. 152—153°/2·5 mm. [d] By-products from residue after distillation. [e] Obtained by hydrolysis (10% KOH in EtOH; 5 hr. reflux). [f] Suspension of carbonyl compound in the ArH added to H_2SO_4. [g] From the same reactants with stannic chloride Bistrzycki and Wehrbein (*Ber.*, 1901, **34**, 3080) obtained diphenyl-*p*-tolylacetic acid. [h] Known compound. [i] Same product obtained in slightly lower yield at room temperature. [k] Phenyl*cyclo*hexane. [l] Ref. 3. [m] Kovache, *Ann. Chim. Phys.*, 1919, **10**, 198. [n] Bistrzycki and Mauron, *Ber.*, 1907, **40**, 4062. [p] Bistrzycki and Gyr, *Ber.*, 1904, **37**, 656, 663.

Method.—The carbonyl compound was first slowly added, with cooling and stirring, to the concentrated sulphuric acid. The aromatic hydrocarbon was added to the mixture at the temperature stated in the Table. Stirring was continued for 0·5—3 hr. more. The mixture

[5] Peters, Griffith, Briggs, and French, *J. Amer. Chem. Soc.*, 1925, **47**, 453.

was poured on ice. The product was separated from the acid mixture by filtration or by extraction and purified by crystallisation or distillation *in vacuo*.

The optimal temperature for the condensation varied with compounds of different reactivity. Toluene and pyruvic acid at −11° to −7° gave up to 38% yields of αα-di-*p*-tolylpropionic acid; at 0—5°, yields of up to 80% of 1 : 1-di-*p*-tolylethylene were obtained. With benzene and pyruvic acid at low temperatures the benzene freezes and there is no reaction, whereas at 5° the yield of αα-diphenylpropionic acid [m. p. 172° (from dilute ethanol); lit.,[1] 171—172°] is only 10—12%, some 1 : 1-diphenylethylene being also formed.

Attempted Decarbonylation of αα-Diarylpropionic Acids.—Decarbonylation of the αα-diarylpropionic acids could be carried out only in concentrated sulphuric acid, in heterogeneous mixtures. In a desire to determine the kinetics, we studied homogeneous solutions, namely, in ethanol containing up to 25% (vol.) of sulphuric acid, in acetic acid containing up to 50% of sulphuric acid, and 1 : 1 (vol.) perchloric acid (70%)–ethanol, but there was no gas evolution up to 70°.

Attempted Reaction of Other Dicarbonyl Compounds with Toluene.—No analogous reaction was observed with toluene and acetylacetone, ethyl acetoacetate, diacetyl, benzil, or pyruvoylbenzene: the starting materials were partly recovered, and partly non-crystallisable gums were obtained which gave neither oximes nor 2 : 4-dinitrophenylhydrazones. Pyruvoylbenzene gave a small amount of benzoic acid.

Discussion

In the conditions used it is most probable that the reaction takes place by an ionic mechanism. Similar Friedel–Crafts type electrophilic substitutions of aromatic compounds by 2-keto-acids have been described. *E.g.*, benzoylformic acid reacts with benzene or toluene, in the presence of aluminium chloride, to give benzilic or 4-methylbenzilic acid, which then reacts further.[6]

Aluminium chloride seems to be a much stronger and much less discriminating catalyst than sulphuric acid. Practically any carbonyl group in a ketone, acid, acid chloride, ester, etc., can be used [7] as the source of an electrophilic reagent to attack aromatic compounds in the presence of aluminium chloride. On the other hand, in the presence of sulphuric acid, the same groups react much more slowly, if at all, giving generally very poor yields. *E.g.*, acetoacetic ester reacts with phenol, with aluminium chloride as the catalyst, to give a 30—40% yield of 4-methylcoumarin, but only 3% in the presence of sulphuric acid; [8] and less reactive aromatic compounds, such as toluene or benzene, seem not to react at all in the presence of sulphuric acid.

In our experiments, we obtained no products from toluene with ethyl acetoacetate, acetylacetone, or benzil. Similarly, simple esters, which in the presence of aluminium chloride give a mixture of acylated and alkylated products [9] with benzene, seem not to react in the presence of sulphuric acid.

It can safely be assumed that the first step in the reaction of 2-keto-acids and esters is protonation. As the ketone-carbonyl group is a stronger base in sulphuric acid than the carboxyl group,[10] the subsequent reaction takes place on the ketone-carbon atom only. We believe that the following mechanism is in accordance with the experimental facts, although other interpretations may also be possible:

(1) $R{\cdot}CO{\cdot}CO_2R' + H^+ \rightleftharpoons {}^+HO{=}CR{\cdot}CO_2R' \longleftrightarrow HO{\cdot}{}^+CR{\cdot}CO_2R'$

(2) $HO{\cdot}{}^+CR{\cdot}CO_2R' + ArH \longrightarrow HO{\cdot}CRAr{\cdot}CO_2R' + H^+$

(3) $HO{\cdot}CRAr{\cdot}CO_2R' + H^+ \rightleftharpoons {}^+H_2O{\cdot}CRAr{\cdot}CO_2R'$

(4) $^+H_2O{\cdot}CRAr{\cdot}CO_2R' \longrightarrow {}^+CRAr{\cdot}CO_2R' + H_2O$

(5) $^+CRAr{\cdot}CO_2R' + ArH \longrightarrow CRAr_2{\cdot}CO_2R' + H^+$

[6] Vorlander and Pritsche, *Ber.*, 1913, **46**, 1793.
[7] See Thomas, "Anhydrous Aluminium Chloride in Organic Chemistry," Reinhold Publ. Co., New York, 1941, pp. 493—497, 632—639, 673–680.
[8] Sethna, Shah, and Shah, *Current Sci.*, 1937, **6**, 93.
[9] Ref. 6, pp. 673—674.
[10] Wiles, *J.*, 1953, 996.

XUM

In the case of pyruvic acid derivatives, a second mechanism involving the enol-form of the 2-keto-acid could be postulated:

$$Me{\cdot}CO{\cdot}CO_2R \rightleftharpoons CH_2{=}C(OH){\cdot}CO_2R \xrightarrow{H^+} CH_2{=}C(OH_2^+){\cdot}CO_2R \xrightarrow{-H_2O} CH_2{=}{}^+C{\cdot}CO_2R \xrightarrow{ArH}$$

$$CH_2{=}CAr{\cdot}CO_2R \xrightarrow{H^+} {}^+CMeAr{\cdot}CO_2R \xrightarrow{ArH} CMeAr_2{\cdot}CO_2R$$

The probability of the existence of enolic forms in concentrated sulphuric acid should be rather low. Moreover, it is excluded for benzoylformic acid and ester, which have no hydrogen atom available for the enolisation. Accordingly, as there seems to be no reason to believe that benzoylformic acid should react by a different mechanism than pyruvic acid, we believe that the mechanism described by steps 1—5 is correct.

Further support is found in the similar reactions of benzilic and atrolactic acid, which exchange their hydroxyl group for a further aryl group.

It is interesting that Bistrzycki [3] found that pyruvic acid reacts normally with 2 mols. of *o*- and *m*-xylene, but only with 1 mol. of *p*-xylene. We verified this and obtained, as he did, α-(2 : 5-dimethylphenyl)acrylic acid as the only product from *p*-xylene. It seems that in this case dehydration of the product of step (3) interrupts and finishes the reaction sequence, double-bond formation by elimination of a proton being much faster in this case than attack of the carbonium ion on a second *p*-xylene molecule. Models of compounds (I, II, and III) show that only the *o*-methyl group causes steric hindrance and the same will be true for replacement of the hydroxyl group by a second aromatic ring. The difference in behaviour between the 2 : 4- (II) and the 2 : 5-compound (III), therefore,

$$\underset{\text{OH}}{\overset{|}{\text{Ar}{\cdot}\text{C}}}\text{Me}{\cdot}CO_2R$$

(I) Ar = 3 : 4-$C_6H_3Me_2$ (II) 2 : 4-$C_6H_3Me_2$ (III) 2 : 5-$C_6H_3Me_2$

cannot be due to steric factors. On the other hand, considerable differences are known to exist between the reactivity of *o*-, *m*-, and *p*-xylene in electrophilic substitutions. Condon [11] showed that the relative rates of the chlorination are $4{\cdot}6 \times 10^3$ for *o*-xylene, $4{\cdot}3 \times 10^5$ for *m*-xylene and $2{\cdot}2 \times 10^3$ for *p*-xylene (benzene = 1). Probably, therefore, the reaction of compound (I) with an additional *o*-xylene molecule takes place easily, there being no steric hindrance, whereas the reaction of the isomer (II) with a second *m*-xylene molecule is still possible, owing to the large relative reactivity of the *m*-xylene molecule, which is enough to counteract the steric hindrance caused by the *o*-methyl group. On the other hand, the same steric hindrance in the reaction of isomer (III) with a second *p*-xylene molecule, the reactivity of which is only 1/200th that of *m*-xylene, seems to be sufficient to slow the reaction so as to allow the elimination of a proton from the carbonium ion corresponding to (III) to be the dominating reaction.

There remains the question why only the $R{\cdot}CO{\cdot}CO_2R'$ system reacts and the formally similar $R{\cdot}CO{\cdot}CO{\cdot}R'$ does not (although, *e.g.*, diacetyl reacts easily with aromatic compounds in the presence of aluminium chloride [12]). We are able to put forward only a tentative explanation: in α-keto-acids and esters there exists the possibility of hydrogen-bond formation between the protonated keto-group and the OH or OR group of the acid or ester. This may stabilise the carbonium ion, with the positive charge on the ketone-carbon atom as in (IV), which is one of the contributing resonance forms of the protonated

(IV) $\underset{R{\cdot}{}^+C\text{———}CO}{\overset{O\cdots H\cdots OR}{|\qquad\quad|}}$ $\underset{R{\cdot}C\text{———}CO}{\overset{{}^+O\cdots H\cdots OR}{\|\qquad\quad|}}$ (V)

keto-ester (V). This type of stabilisation should be absent in 1 : 2-diketones, where the carbonyl groups are in their most stable conformation when the distance between the two oxygen atoms is at a maximum and where there should be no possibility of intramolecular hydrogen bonding.

Department of Organic Chemistry A, The Hebrew University,
Jerusalem, Israel. [*Received, March 25th*, 1958.]

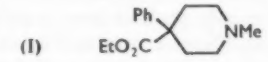
[11] Condon, *J. Amer. Chem. Soc.*, 1948, **70**, 1963; see also Brown and McGary, *ibid.*, 1955, **77**, 2310.
[12] Wegmann and Dahn, *Helv. Chim. Acta*, 1946, **29**, 101.

621. *Some New Analogues of Pethidine. Part II.*[1] *Alkoxyalkylnorpethidines.**

By P. M. Frearson and E. S. Stern.

Alkylation of ethyl 4-phenylpiperidine-4-carboxylate with ω-chloroalkyl alkyl ethers has given a new series of substances related to pethidine, some of which are potent analgesics. Structure–activity relations within this series of alkoxyalkylnorpethidines have been examined and alkylthio-analogues prepared for comparison.

In Part I,[1] a series of analogues (II) of pethidine (I) was reported, where Y represented an alkyl chain and X a nitrogenous heterocyclic residue. Of the substances tested, only those carrying a morpholino- (or tetrahydro-1 : 4-thiazin-4-yl) ring (for X in Formula II) had



(I)

(II)

marked analgesic potency;[2] the close analogues in which the oxygen (or sulphur) atom of this residue was replaced by carbon or nitrogen were almost inactive. Clearly, the presence of this oxygen atom was desirable in this series of pethidine analogues, although it is chemically inert and at some distance from the part of the molecule normally considered to be active.

These findings and deductions led to the synthesis of further analogues of pethidine, again formulated as (II) and derived from norpethidine (ethyl 4-phenylpiperidine-4-carboxylate), Y representing an alkyl chain and X an alkyl group bearing an oxygenated function. When this work started (1955), only one such substance had been reported,[3] namely, 2-hydroxyethylnorpethidine[4] (II; Y = CH_2·CH_2, X = OH), which was rather less active than pethidine (I). Recently, two further oxygenated derivatives of norpethidine, namely, (II; Y = CH_2·CHPh, X = OH and OAc, respectively) were synthesised and tested,[5] and the secondary alcohol (II; Y = CH_2·CHPh, X = OH) was shown to be about three times as potent as pethidine; its acetate ester, surprisingly, was almost inactive.

The present paper deals with aliphatic ethers (II; Y = alkyl, X = alkoxy) derived from norpethidine. It was found that some of these ethers exceeded pethidine in analgesic potency, and an attempt was then made—by varying the alkyl and alkoxy groupings—to establish the optimum position of the oxygen atom with respect to the heterocyclic residue.

Norpethidine was readily alkylated by ω-chloroalkyl alkyl ethers in, *e.g.*, ethyl or pentyl alcohol. The intermediate chloroalkyl alkyl ethers were generally prepared from the alkyl hydroxyalkyl ethers (alkylene glycol monoethers) some of which were commercially available. In the preparation of ω-chlorobutyl ethyl ether the attempted conversion of tetramethylene chlorohydrin into ethyl hydroxybutyl ether resulted in cyclisation to tetrahydrofuran; it was necessary, therefore, to protect the hydroxyl group of the chlorohydrin: this was accomplished by addition of 2 : 3-dihydropyran before etherification, and similar work has since been published.[6]

The alkoxyalkylnorpethidines prepared are listed in Tables 1 and 2; they were high-boiling, fairly viscous bases, some of which began to crystallise on prolonged storage. They dissolved very readily in mineral acids, but the salts were very soluble in water and alcohol, and hygroscopic when precipitated from solution by ether or light petroleum. Only

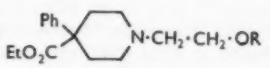
* Some of the work reported forms part of B.P. Applns. 34,051/55 and 4965/57.

[1] Part I, Anderson, Frearson, and Stern, *J.*, 1956, 4088.
[2] Millar and Stephenson, *Brit. J. Pharmacol.*, 1956, **11**, 27.
[3] Cf. Braenden, Eddy, and Halbach, *Bull. World Health Organisation*, 1955, **13**, 937.
[4] Schaumann, *Arch. Path. Pharmakol.*, 1940, **196**, 127.
[5] Perrine and Eddy, *J. Org. Chem.*, 1956, **21**, 125.
[6] Crisan, *Ann. Chim.* (*France*), 1956, **1**, 436.

ethoxypropylnorpethidine (No. 6) afforded a well-crystallised hydrobromide suitable for characterisation; the alkoxyalkylnorpethidines (Table 1), however, gave readily crystallisable picrates. For characterisation of ethoxybutyl- and ethoxypentyl-norpethidine (Nos. 7 and 8) the methiodides were prepared.

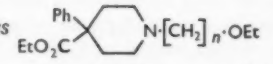
For comparison with these oxygenated substances, methylthio- and ethylthio-ethylnorpethidine (II; Y = $CH_2 \cdot CH_2$, X = SMe and SEt, respectively) were prepared. These were readily distillable oils which differed from the oxygen analogues in giving highly crystalline hydrobromides, very suitable for characterisation.

TABLE 1. *Alkoxyethylnorpethidines*



No.	R	B. p./mm.	n_D^{20}	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
1	Me	135—140°/1	1·5152	$C_{17}H_{25}O_3N$	69·9	8·9	4·35	70·05	8·6	4·8
2	Et	166—168°/1—1·5	1·5111	$C_{18}H_{27}O_3N$	71·2	9·0	4·35	70·8	8·9	4·6
3	Pr^n	170—180°/0·8	1·5079	$C_{19}H_{29}O_3N$	71·55	9·0	4·25	71·45	9·15	4·4
4	Pr^i	170—180°/1	1·5050	$C_{19}H_{29}O_3N$	71·65	9·15	4·3	71·45	9·15	4·4
5	Bu^n	185—190°/1	1·5050	$C_{20}H_{31}O_3N$	71·95	9·45	3·95	72·05	9·35	4·2

Table 2. *Ethoxyalkylnorpethidines*



No.	n	B. p./mm.	n_D^{20}	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
2	2	See Table 1								
6	3	185°/2	1·5083	$C_{19}H_{29}O_3N$	72·0	9·25	3·95	71·45	9·15	4·4
7	4	180°/1	1·5068	$C_{20}H_{31}O_3N$	72·2	9·35	4·25	72·05	9·35	4·2
8	5	195°/0·6	1·5072	$C_{21}H_{33}O_3N$	72·25	9·5	4·35	72·55	9·55	4·05
9	6	185°/0·5	1·5052	$C_{22}H_{35}O_3N$	73·2	9·6	4·4	73·1	9·75	3·9

Pharmacological tests are being reported in detail elsewhere [7]: they established that the ethoxyalkylnorpethidines (II; Y = $[CH_2]_n$, X = OEt; cf. Table 2) have high analgesic potency: the potency of the 4-aminobutanol derivative (substance No. 7, when n is 4) is approximately ten times that of pethidine and that of the ethanolamine derivative (substance No. 2, when n is 2) is approximately 5 times that of pethidine. Analgesic potency is lower (about equal to that of pethidine) when n is 3, 5, or 6 (substances No. 6, 8, and 9). It is remarkable, though not necessarily significant, that certain other simple derivatives of 4-aminobutanol and of ethanolamine have interesting pharmacological properties.[8]

In the series of alkoxyethylnorpethidines (II; Y = $CH_2 \cdot CH_2$; X = OR; cf. Table 1) analgesic acitivity was greatest for the ethoxyethyl compound (No. 2); the *iso*propoxy-compound (No. 4) had about half and the other ethers one-third of this activity. Methylthio- and ethylthio-ethylnorpethidine were considerably less active.

EXPERIMENTAL

Intermediates.—2-Chloroethyl ethyl ether had b. p. 109—110°, n_D^{20} 1·4122 (Heilbron and Bunbury [9] quote b. p. 107—108°, n_D^{20} 1·4113). 3-Chloropropyl ethyl ether had b. p. 129—130°, n_D^{20} 1·4162 (Smith and Sprung [10] give b. p. 125—128°; Pishnamazzade [11] gives b. p. 128—136°, n_D^{20} 1·4119). 4-Chlorobutyl ethyl ether was prepared from tetramethylene chlorohydrin. Action of dihydropyran (Copelin's method [12]) gave 4-chlorobutyl tetrahydropyran-2-yl ether, b. p. 93—94°/3 mm., n_D^{20} 1·4608 (Copelin gives b. p. 105°/10 mm.; Crisan [6] gives b. p. 114°/12 mm., n_D^{22} 1·4596), which with sodium ethoxide (1 equiv.) in ethanol gave 4-ethoxybutyl tetrahydropyran-2-yl ether,

[7] Blair and Stephenson, *Brit. J. Pharmacol.*, in the press.

[8] Cf. Lunsford, Murphey, and Rose, *J. Org. Chem.*, 1957, **22**, 1225; Kuehl, Jacob, Ganley, Ormond, and Meisinger, *J. Amer. Chem. Soc.*, 1957, **79**, 5577.

[9] Heilbron and Bunbury's "Dictionary of Organic Compounds," Eyre and Spottiswoode, London, 1943.

[10] Smith and Sprung, *J. Amer. Chem. Soc.*, 1943, **65**, 1276.

[11] Pishnamazzade, *Trudy Inst. khim. Akad. Nauk Azerbaidzhan*, 1954, **13**, 49; *Chem. Abs.*, 1955, **49**, 9481.

[12] Copelin, U.S.P. 2,541,747.

b. p. 125—130°/20 mm., n_D^{20} 1·4440 (Found: C, 64·7; H, 10·7. Calc. for $C_{11}H_{22}O_3$: C, 65·3; H, 10·95%) (Crisan [6] gives b. p. 118°/12 mm., n_D^{22} 1·4400). This ether was hydrolysed by boiling 2N-hydrochloric acid to 4-ethoxybutanol, b. p. 76—80°/14 mm., n_D^{20} 1·4242 (Crisan [6] gives b. p. 83°/16 mm., n_D^{20} 1·4229; Palomaa and Jansson [13] give b. p. 72°/8 mm., n_D^{20} 1·4229), converted by thionyl chloride into the desired 4-*chlorobutyl ethyl ether*, b. p. 142°, n_D^{20} 1·4244 (Found: C, 52·85; H, 9·35. $C_6H_{13}OCl$ requires C, 52·75; H, 9·6%). 5-*Chloropentyl ethyl ether*, prepared by action of thionyl chloride on 5-ethoxypentanol,[13] had b. p. 72°/17 mm., n_D^{20} 1·4300 (Found : C, 55·55; H, 10·05; Cl, 23·3. $C_7H_{15}OCl$ requires C, 55·8; H, 10·05; Cl, 23·55%). 6-Bromohexyl ethyl ether, prepared by action of sodium ethoxide on hexamethylene dibromide, had b. p. 64°/1 mm., n_D^{20} 1·444 (Dionneau [14] gives b. p. 121—123°/35 mm.). 2-Chloroethyl methyl ether had b. p. 88·5—89°, n_D^{20} 1·4112 (Karvonen [15] gives b. p. 89·4—89·7°/763 mm., n_D^{20} 1·4111). 2-Chloroethyl *n*-propyl ether had b. p. 131—134°, n_D^{20} 1·4188 (Karvonen [15] gives b. p. 130°/756 mm., n_D^{20} 1·4176). 2-*Chloroethyl* iso*propyl ether* had b. p. 118—120°/754 mm., n_D^{20} 1·4125 (Found: C, 49·05; H, 9·0. $C_5H_{11}OCl$ requires C, 49·0; H, 9·05%). *n*-Butyl 2-chloroethyl ether had b. p. 148—152°, n_D^{20} 1·4235 (Chalmers [16] gives b. p. 153—154°, but Sklyarov [17] gives b. p. 139—141°, n_D^{20} 1·4310). 2-Chloroethyl methyl sulphide had b. p. *ca.* 55°/30 mm., n_D^{20} 1·4970 (Kirner [18] gives b. p. 55—56°/30 mm., n_D^{20} 1·4902). 2-Chloroethyl ethyl sulphide had b. p. 80—84°/82 mm., n_D^{20} 1·4890 (Thompson *et al.*[19] give b. p. 55—58°/22 mm.).

Preparation and Characterisation of Tertiary Bases.—In a typical experiment, norpethidine (5 g.), m. p. *ca.* 33°, and 2-chloroethyl methyl ether (5·5 g.) were refluxed in pentyl alcohol (20 ml.) over sodium carbonate (2 g.) for about 30 hr. The solution was filtered and the filtrate distilled, giving, as high-boiling fraction, ethyl 1-2′-methoxyethyl-4-phenylpiperidine-4-carboxylate (No. 1 in Table 1) (*ca.* 4·5 g.).

Ethyl 1-2′-*methylthioethyl*-4-*phenylpiperidine*-4-*carboxylate*, prepared from norpethidine and chloroethyl methyl sulphide, had b. p. 174—175°/0·5—1 mm., n_D^{20} 1·5402 (Found: C, 66·7; H, 7·6; N, 4·15. $C_{17}H_{25}O_2NS$ requires C, 66·4; H, 8·2; N, 4·55%). The *hydrobromide*, recrystallised from aqueous alcohol, had m. p. 197° (Found: C, 52·45; H, 6·65; N, 3·5. $C_{17}H_{25}O_2NS$,HBr requires C, 52·6; H, 6·75; N, 3·6%).

Ethyl 1-2′-*ethylthioethyl*-4-*phenylpiperidine*-4-*carboxylate* had b. p. 180—185°/0·5—1 mm., n_D^{20} 1·5370 (Found: C, 67·15; H, 8·3; N, 4·15. $C_{18}H_{27}O_2NS$ requires C, 67·25; H, 8·45; N, 4·35%). The *hydrobromide* had m. p. 183° (Found: C, 54·3; H, 6·85; N, 3·4. $C_{18}H_{27}O_2NS$,HBr requires C, 53·75; H, 7·0; N, 3·5%).

The bases described in Tables 1 and 2 were characterised as follows: *Ethyl* 1-2′-*ethoxyethyl*-4-*phenylpiperidine*-4-*carboxylate* (No. 2) had pK_a 7·45 and gave a *picrate* which, crystallised from ethanol, had m. p. 86° (Found: C, 53·4; H, 5·6; N, 10·2. $C_{18}H_{27}O_3N,C_6H_3O_7N_3$ requires C, 53·95; H, 5·65; N, 10·45%). Ethyl 1-3′-ethoxypropyl-4-phenylpiperidine-4-carboxylate (No. 6) gave the *hydrobromide*, m. p. 130—131° (from ethanol) (Found: C, 56·85; H, 7·45; N, 3·3; Br, 20·05. $C_{19}H_{29}O_3N$,HBr requires C, 56·9; H, 7·55; N, 3·5; Br, 19·95%). Ethyl 1-4′-ethoxybutyl-4-phenylpiperidine-4-carboxylate (No. 7) had pK_a 7·7 and gave a *methiodide*, m. p. 120—122° (from ethyl acetate) (Found: C, 52·9; H, 7·0; N, 2·8. $C_{21}H_{34}O_2NI$ requires C, 53·05; H, 7·2; N, 2·95%). Ethyl 1-5′-ethoxypentyl-4-phenylpiperidine-4-carboxylate (No. 8) gave the *methiodide* (from ethyl acetate), m. p. 152—154° (Found: C, 53·65; H, 7·2; N, 2·5. $C_{22}H_{36}O_3NI$ requires C, 54·0; H, 7·4; N, 2·85%). Ethyl 2-methoxyethyl-4-phenylpiperidine-4-carboxylate (No. 1) was characterised as *picrate*, m. p. 70—71° (from ethanol–light petroleum (Found: N, 11·05. $C_{17}H_{25}O_3N,C_6H_3O_7N$ requires N, 10·75%); ethyl (2-*n*-propoxyethyl)- and ethyl (2-*iso*propoxyethyl)-4-phenylpiperidine-4-carboxylate (Nos. 3 and 4 respectively) as *picrates* (from ethyl acetate–light petroleum) of m. p. 124° (Found: N, 10·1. $C_{19}H_{29}O_3N,C_6H_3O_7N$ requires N, 10·2%) and m. p. 108° (Found: N, 10·4%), respectively; and ethyl (2-*n*-butoxyethyl)-4-phenylpiperidine-4-carboxylate (No. 5) as *picrate*, m. p. 125° (from ethyl acetate–light petroleum) (Found: N, 9·9. $C_{20}H_{31}O_3N,C_6H_3O_7N_3$ requires N, 9·9%).

RESEARCH DEPARTMENT, J. F. MACFARLAN & CO. LTD.,
EDINBURGH, 8.

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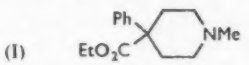
[13] Palomaa and Jansson, *Ber.*, 1931, **64**, 1606.
[14] Dionneau, *Compt. rend.*, 1881, **142**, 92.
[15] Karvonen, *Ann. Acad. Sci. Fennicae*, 1912, **3**, *A*, No. 7, p. 1. *Chem. Zentr.*, 1912, II, 1270.
[16] Chalmers, *Canad. J. Res.*, 1932, **7**, 464.
[17] Sklyarov, *J. Gen. Chem. U.S.S.R.*, 1939, **9**, 2121.
[18] Kirner, *J. Amer. Chem. Soc.*, 1928, **50**, 2446.
[19] Thompson, Chenicek, and Symon, *Ind. Eng. Chem.*, 1952, **44**, 1659.

622. *Some New Analogues of Pethidine. Part III.*[1] *1-Aryloxyalkylnorpethidines, and Close Analogues.**

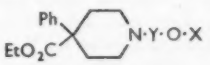
By P. M. Frearson and E. S. Stern.

The preparation of further pethidine derivatives, by alkylation of norpethidine with aryl chloroethyl ethers, is described. The phenylthioethyl, *cyclo*hexyloxyethyl, benzyloxyethyl, and phenoxybutyl analogues were prepared for comparison. Some of the substances have high analgesic potency.

The present paper describes the preparation of analogues of pethidine (I) with the general formula (II), in which Y represents $[CH_2]_2$ or $[CH_2]_4$ and X is an aryl or an aralkyl group, linked to Y by an oxygen atom. Such analogues of pethidine have not been reported before, but the preparation of and tests on phenethyl-[2] and *p*-aminophenethyl-norpethidine,[3] closely related to the present series of compounds but lacking the ether grouping, were reported while the present work was in progress.



(I)



(II)

Ethyl 1-2′-phenoxyethyl-4-phenylpiperidine-4-carboxylate was readily obtained on alkylation of norpethidine (II; Y·O·X = H) with 2-phenoxyethyl chloride in, *e.g.*, ethanol or pentyl alcohol. The product was isolated as the hydrobromide from the reaction mixture after removal of solvent; the hydrobromide was sparingly soluble in water, but more soluble in alcohol. For comparison with this phenyl ether, the phenylthio-compound and the *cyclo*hexyl ether were also prepared. The aryl-substituted phenoxyethyl analogues listed in the Table were similarly prepared for pharmacological evaluation of substituent effects.

No unexpected difficulties were encountered in the preparations but *o*-substitution made condensation and isolation of the products more difficult; the *o*-chlorophenoxyethyl analogue, for instance, could not be obtained pure, and the *o*-methoxyphenoxyethyl analogue was obtainable in poor yield only.

The intermediate aryl chloroethyl ethers were prepared by one of three methods: (*a*) the phenol in form of its sodio-derivative was treated with ethylene dichloride: yields by this method were not very good; (*b*) the phenol in form of its sodio-derivative was treated with ethylene chlorohydrin and the glycol monoether then converted into the desired intermediate by means of thionyl chloride; (*c*) the phenol was treated with aqueous sodium hydroxide and with 2-chloroethyl benzenesulphonate—this method[4] was particularly useful in the preparation of naphthyloxyethyl chloride.

Pharmacological tests are being reported in detail elsewhere.[5] The tests showed that the phenoxyethyl- (II; $Y = CH_2{\cdot}CH_2$, X = Ph), phenoxybutyl- (II; $Y = [CH_2]_4$, X = Ph), and benzyloxyethyl-norpethidines (II; $Y = CH_2{\cdot}CH_2$, $X = CH_2Ph$) were highly active as analgesics; they were about 5—10 times as potent as pethidine. Further substitution in the aromatic ring reduced, or in some cases abolished, the analgesic potency. Ethyl 1-2′-phenylthioethyl- and ethyl 1-2′-*cyclo*hexyloxyethyl-4-phenylpiperidine-4-carboxylate were both much less active than the phenoxyethyl analogue, although their potency appeared to be somewhat greater than that of pethidine; the 2-naphthyloxyethyl compound had little analgesic potency.

The final stages of these investigations will be reported later.

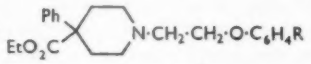
* Some of this work forms part of B.P. Applns. 34,051/55 and 4965/57.

[1] Part II, preceding paper.
[2] Perrine and Eddy, *J. Org. Chem.*, 1956, **21**, 125.
[3] Weijlard, Orahovats, Sullivan, Purdue, Heath, and Pfister, *J. Amer. Chem. Soc.*, 1956, **78**, 2342.
[4] Herbst and Johnson, *J. Org. Chem.*, 1952, **17**, 693.
[5] Blair and Stephenson, *Brit. J. Pharmacol.*, in the press.

Experimental

Intermediates.—2-Phenoxyethyl chloride had m. p. >25°, b. p. 108—110°/16 mm. (Bentley *et al.*[6] give m. p. 28°, b. p. 220°). 2-cyclo*Hexyloxyethyl chloride*, prepared from 2-*cyclo*hexyloxyethanol,[7] b. p. 105°/20 mm., n_D^{20} 1·4648, had b. p. 82—84°/16 mm., n_D^{20} 1·4636 (Found: C, 59·5; H, 9·2. $C_8H_{15}OCl$ requires C, 59·1; H, 9·3%). 2-Phenylthioethyl chloride had b. p. 140—141°/30 mm., n_D^{20} 1·5845 (Price and Morita [8] give b. p. 114—115°/1 mm.). 2-*o*-Tolyloxyethyl chloride had b. p. 118—120°/120 mm., n_D^{20} 1·5292 (Harris and Stewart [9] give b. p. 230—231°); 2-*m*- and 2-*p*-tolyloxyethyl chloride had b. p. 125—126°/20 mm., n_D^{20} 1·5294, and m. p. 35—36°, b. p. 127—128°/20 mm., respectively (Harris and Stewart [9] give b. p. 235—236° and 236—237°, respectively). 2-m-*Chlorophenoxyethyl chloride* had b. p. 128—130°/18 mm., n_D^{20} 1·5478 (Found: C, 49·9; H, 4·25. $C_8H_8OCl_2$ requires C, 50·3; H, 4·25%), and the 2-p-*chloro-isomer* had m. p. 34—35°, b. p. 135°/20 mm. (Found: C, 50·25; H, 4·65%); these were prepared from the corresponding 2-chlorophenoxyethanol.[10] 2-o-*Nitrophenoxyethyl chloride* had m. p. 35·5—36·5° (Found: C, 47·15; H, 4·0; N, 6·85. $C_8H_8O_3NCl$ requires C, 47·65; H, 4·0; N, 6·95%); the *m*- and *p*-isomers had, respectively, m. p. 59—60° (Found: C, 47·6; H, 4·0; N, 7·4%), and m. p. 47—48°, b. p. 204—206°/25 mm. (Katrak [11] gives m. p. 67—68° for the *p*-nitro-isomer). 2-*o*-Methoxyphenoxyethyl chloride had m. p. 40°, b. p. 138°/30 mm. (Harris and Stewart [9] give b. p. 254—255°); 2-*m*- and 2-*p*-methoxyphenoxyethyl chloride had b. p. 146—147°/15 mm., n_D^{20} 1·5380 (Motwani and Wheeler [12] give b. p. 130°/5 mm.), and m. p. 44—45° (Harris and Stewart [9] give b. p. 286—287°), respectively. 2-*p*-Acetamidophenoxyethyl chloride had m. p. 119° (Harris and Stewart [9] give b. p. 230—231°). 2-p-*Ethoxycarbonylphenoxyethyl chloride* (prepared from the alcohol [13]) had m. p. 68—70° (Found: C, 57·55; H, 5·7. $C_{11}H_{13}O_3Cl$ requires C, 57·75; H, 5·75%). p-*Diphenylyloxyethyl chloride*, crystallised from alcohol, had

Hydrobromides of substituted phenoxyethylnorpethidines



		Found (%)					Required (%)			
R	M. p.	C	H	N	Br	Formula	C	H	N	Br
H [a]	156·5—157·5°	60·4	6·35	3·2	18·7	$C_{22}H_{27}O_2N,HBr$	60·8	6·5	3·25	18·4
o-Me [b]	168—170°	61·65	6·8	3·2	—	$C_{23}H_{29}O_2N,HBr$	61·6	6·75	3·1	—
m-Me	168—169°	61·85	6·8	2·75	—	$C_{23}H_{29}O_2N,HBr$	61·6	6·75	3·1	—
p-Me [c]	145—146°	61·9	6·4	3·2	—	$C_{23}H_{29}O_2N,HBr$	61·6	6·75	3·1	—
m-Cl	170—171°	56·25	5·95	2·65	—	$C_{22}H_{26}O_2NCl,HBr$	56·35	5·8	3·0	—
p-Cl [d]	180°	56·7	5·9	2·75	—	$C_{22}H_{26}O_2NCl,HBr$	56·35	5·8	3·0	—
o-NO_2	171—172°	55·1	5·7	5·7	—	$C_{22}H_{26}O_4N_2,HBr$	55·1	5·7	5·85	—
m-NO_2	194—195°	55·45	5·75	5·3	—	$C_{22}H_{26}O_4N_2,HBr$	55·1	5·7	5·85	—
p-NO_2 [e]	186—187°	55·05	5·65	5·25	—	$C_{22}H_{26}O_4N_2,HBr$	55·1	5·7	5·85	—
m-MeO	171—172°	59·8	6·8	3·2	16·7	$C_{23}H_{29}O_3N,HBr$	59·5	6·5	3·0	17·2
p-MeO	180—182°	59·6	6·45	3·2	—	$C_{23}H_{29}O_3N,HBr$	59·5	6·5	3·0	—
p-NHAc	220—221°	58·75	6·55	5·25	16·75	$C_{24}H_{30}O_3N_2,HBr$	58·65	6·35	5·7	16·25
p-CO_2Et	190—191°	59·7	6·2	2·75	—	$C_{25}H_{31}O_5N,HBr$	59·3	6·35	2·75	—
p-Ph	170°	65·55	6·4	2·9	—	$C_{28}H_{31}O_2N,HBr$	65·85	6·4	2·75	—

[a] Hydrochloride, m. p. 156° (from alcohol). [b] Hydrochloride, m. p. 130°. [c] Hydrochloride, m. p. 167°. [d] Hydrochloride, m. p. 178°. [e] Base, m. p. 89° (from light petroleum–ethyl acetate).

m. p. 103—104° (Found: C, 72·35; H, 5·75. $C_{14}H_{13}OCl$ requires C, 72·25; H, 5·65); it was prepared from the alcohol.[14] 2-2′-Naphthyloxyethyl chloride had m. p. 81—82° (Herbst and Johnson [4] give m. p. 79—80°). 2-Benzyloxyethyl chloride had b. p. 112°/10 mm., n_D^{20} 1·5225 (Bennett [15] gives b. p. 124°/20 mm.). 4-Phenoxybutyl chloride had b. p. 144°/20 mm., n_D^{20} 1·5230 (Kharash *et al.*[16] give b. p. 133—134°/9 mm.), and was obtained in high yield from

[6] Bentley, Haworth, and Perkin, *J.*, 1896, **69**, 161.
[7] Mousseron, Jacquier, Mousseron-Canet, and Zagdoun, *Bull. Soc. chim. France*, 1952, 1042.
[8] Price and Morita, *J. Amer. Chem. Soc.*, 1953, **75**, 4747.
[9] Harris and Stewart, *Canad. J. Res.*, 1949, **27***B*, 739.
[10] Cf. Boyd and Marle, *J.*, 1914, **105**, 2117.
[11] Katrak, *J. Indian Chem. Soc.*, 1936, **13**, 334.
[12] Motwani and Wheeler, *J.*, 1935, 1098.
[13] Sugiyama, Washizu, and Jinno, *J. Chem. Soc. Japan*, 1954, **75**, 545.
[14] Vernon, U.S.P. 2,140,824.
[15] Bennett, *J.*, 1925, **127**, 1277.
[16] Kharasch, Stampa, and Nudenberg, *J. Org. Chem.*, 1953, **18**, 575.

XUM

4-chlorobutanol by action of dihydropyran and etherification of the 2-4′-chlorobutoxytetrahydropyran with sodium phenoxide in alcohol to 2-4′-*phenoxybutoxytetrahydropyran*, b. p. 185°/25 mm., n_D^{20} 1·5080 (Found: C, 71·55; H, 8·45. $C_{15}H_{22}O_3$ requires C, 71·95; H, 8·85%); this was hydrolysed to 4-phenoxybutanol which was treated with thionyl chloride in chloroform.

Tertiary Bases.—Ethyl 4-phenyl-1-2′-phenylthioethylpiperidine-4-carboxylate. In a typical experiment, norpethidine (5 g.) and 2-phenylthioethyl chloride (3·7 g.) were dissolved in pentyl alcohol (25 ml.) and sodium carbonate (1 g.) was added. The mixture was boiled under reflux for 30 hr. and then filtered, and the filtrate was concentrated under reduced pressure. On acidification with 40% aqueous hydrobromic acid, *ethyl 4-phenyl-1-2′-phenylthioethylpiperidine-4-carboxylate hydrobromide* (5·5 g.) crystallised; recrystallised from ethyl acetate–ethanol it had m. p. 178—180° (Found: C, 58·35; H, 6·15; N, 3·4. $C_{22}H_{28}O_2NBrS$ requires C, 58·65; H, 6·30; N, 3·1%). Analogously prepared, and not listed in the Table, were: *ethyl 1-2′-cyclohexyloxyethyl-4-phenylpiperidine-4-carboxylate hydrobromide*, m. p. 123—124° (Found: C, 60·15; H, 7·6; N, 3·2. $C_{22}H_{34}O_3NBr$ requires C, 60·0; H, 7·8; N, 3·2%); *ethyl 1-(2′-2″-naphthyloxyethyl)-4-phenylpiperidine-4-carboxylate hydrobromide*, m. p. 164° (Found: C, 64·45; H, 6·25; N, 2·9. $C_{26}H_{29}O_3N$,HBr requires C, 63·85; H, 6·25; N, 2·9%); *ethyl 1-2′-benzyloxyethyl-4-phenylpiperidine-4-carboxylate hydrobromide*, m. p. 138—139° (Found: C, 61·4; H, 6·6; N, 3·05; Br, 18·3. $C_{23}H_{29}O_3N$,HBr requires C, 61·6; H, 6·75; N, 3·1; Br, 17·85%) (hydrochloride, m. p. 105°); and *ethyl 1-(4′-phenoxybutyl)-4-phenylpiperidine-4-carboxylate hydrobromide*, m. p. 161—162° (Found: C, 61·75; H, 6·85; N, 2·85. $C_{24}H_{32}O_3NBr$ requires C, 62·3; H, 7·0; N, 3·05%).

The authors of this and the preceding paper are grateful to Miss C. I. Dickson for skilled technical assistance, to Mr. F. J. Bolton for his interest, and to the Directors of J. F. Macfarlan & Co. Ltd. for permission to publish the work.

RESEARCH DEPARTMENT, J. F. MACFARLAN & CO. LTD.,
EDINBURGH, 8.

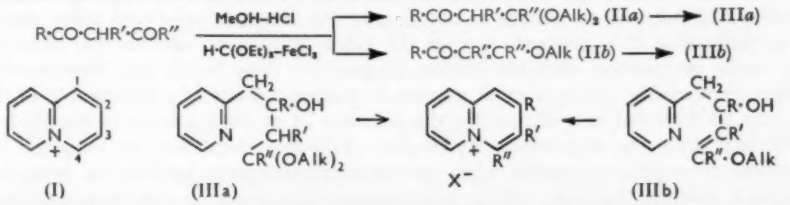
[*Received, March 28th*, 1958.]

623. *Synthesis and Properties of Dehydropyridocolinium Salts.*

By A. RICHARDS and T. S. STEVENS.

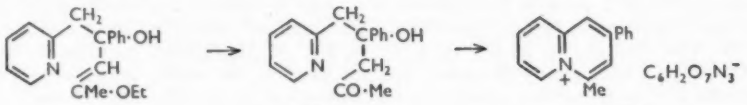
Several dehydropyridocolinium salts (I) have been prepared by treating the enol ether or the monoacetal of a β-diketone with 2-picolyl-lithium and cyclising the resulting alcohol with acid. Their reactions, especially with anionoid reagents, have been examined.

REPLACEMENT by nitrogen of a carbon atom common to both rings of the naphthalene system gives the dehydropyridocolinium ion (I). Salts of this cation were first prepared by Boekelheide and Gall [1] in moderate yield; we have now prepared homologues by a more effective process [2] and studied some of their reactions. The synthetic method was essentially an adaptation of that employed by McLamore and Woodward [3] for the synthesis of sempervirine metho-salts. A β-oxo-aldehyde or -ketone is converted into the monoacetal and/or the enol ether and this treated with picolyl-lithium; the product, usually of low stability and often an unresolved mixture, is cyclised by alcoholic picric acid:



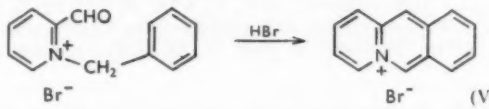
[1] Boekelheide and Gall, *J. Amer. Chem. Soc.*, 1954, **76**, 1832; Boekelheide and Ross, *ibid.*, 1955, **77**, 5691.
[2] Preliminary communication, *Chem. and Ind.*, 1954, 905.
[3] McLamore and Woodward, *J. Amer. Chem. Soc.*, 1949, **71**, 349.

The dehydropyridocolinium salts, assembled in Table 2, are all substituted in position 2, owing to more difficult accessibility of initial materials for those unsubstituted in this position. The method failed in the case (9) of 3-methyl-2-phenyldehydropyridocolinium salts. In case (8) the product of attempted cyclisation with picric acid gave analyses correct for the picrate of the ketone (IV), indicating simple hydrolysis of the enol ether. When refluxed with acetic anhydride and sulphuric acid this product yielded the quaternary picrate (V).



(IV) (V)

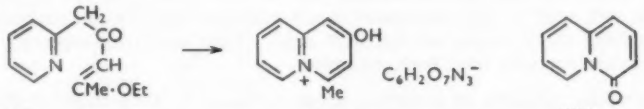
Bradsher and Beavers[4] prepared 2 : 3-benzodehydropyridocolinium bromide by dehydrating pyridine-2-aldehyde benzylobromide:



(VI)

A similar dehydration of the corresponding allylobromide would give an unsubstituted dehydropyridocolinium salt, but we failed to effect this with hydrobromic, sulphuric, or polyphosphoric acid.

In an attempt to prepare a dehydropyridocolinium salt unsubstituted in position 2 by a modified method, ethyl β-ethoxycrotonate was treated with picolyl-lithium, giving (VII). Numerous attempts to reduce the carbonyl group of this compound failed, as did experiments on the simpler 2-acetonylpyridine. With picric acid, the ketone (VII) itself gave an unstable product having the composition of 2-hydroxy-4-methyldehydropyridicolinium picrate (VIII).



(VII) (VIII) (IX)

When the methiodide of pyridine, quinoline, or acridine is treated with silver oxide in water, the quaternary hydroxide reaches equilibrium with the pseudo-base; the ammonium hydroxide predominates in the first case, the pseudo-base in the last. The loss in resonance energy consequent on dearomatisation of a pyridine ring diminishes in the order given, and the pseudo-base further tends, with rising molecular weight, to separate from aqueous solution or to pass into organic solvents. Formation of a pseudo-base from dehydropyridocolinium hydroxide would destroy the aromaticity of both rings, and there was no indication of its production when the iodide in aqueous solution was treated with silver oxide or warmed with 10N-sodium hydroxide. The iodide did, however, reduce alkaline ferricyanide, giving a small amount of material doubtfully identifiable as (IX);[5] this may be regarded as evidence for the presence of at least a trace of pseudo-base in equilibrium with the ammonium hydroxide. Likewise there was no evidence of the formation of a pseudo-cyanide when dehydropyridocolinium iodide was treated with potassium cyanide solution. With *n*-butylmagnesium bromide dehydropyridocolinium iodide gave only a small amount of unstable brown oil; the metho-salts of quinoline and

[4] Bradsher and Beavers, *J. Amer. Chem. Soc.*, 1955, **77**, 4812.
[5] Boekelheide and Lodge, *ibid.*, 1951, **73**, 3681.

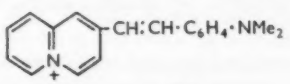
acridine, but not those of pyridine, readily afford *C*-alkyl-*N*-methyl-dihydro-bases with Grignard reagents.

In the case of 3-phenyl-1 : 2-benzodehydropyridocolinium bromide [6] (X), slightly more favourable to production of a pseudo-base, the ammonium hydroxide solution deposited an amorphous benzene-soluble product after 2 days. The compound (X) reduced alkaline ferricyanide, but gave no pseudo-cyanide with sodium cyanide. On the other hand 2 : 3-benzodehydropyridocolinium iodide (as VI) quickly afforded an unstable pseudo-base which was soon oxidised in air, and with sodium cyanide it gave an amorphous product, apparently the pseudo-cyanide. The iodide also reduced alkaline ferricyanide. Unsuccessful attempts were made to induce the pseudo-base to condense, in the same way as berberine, with nitromethane and other " reactive methylene compounds."

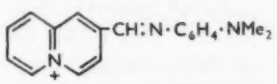
1 : 2-Dimethylquinolinium salts, on treatment with alkali, give 1 : 2-dihydro-1-methyl-2-methylenequinolines, but neither 2-methyl-, 2-ethyl-3-methyl-, nor 2 : 3-dimethyl-dehydropyridocolinium salts behaved in this way, and in other respects they resembled the unsubstituted compound in their behaviour towards anionoid reagents. The methyl group of the 2-methyl compound showed however the reactivity of a 4-methyl substituent in a pyridine ring in condensing with *p*-dimethylaminobenzaldehyde and with *NN*-dimethyl-*p*-nitrosoaniline, giving compounds (XI) and (XII) respectively. These highly coloured products were decolorised reversibly by dilute acids, owing no doubt to exclusion by protonation of the second nitrogen atom from the conjugated system.

(X)

All the dehydropyridocolinium ions studied gave orange, crystalline dibromoiodides, $[B]^+[IBr_2]^-$, when the iodides were treated with bromine in acetic acid. The bright orange compound which Boekelheide and Ross [1] obtained by treating 3 : 4-dihydrodehydropyridocolinium iodide with bromine and formulated as (XIII) closely resembles the original

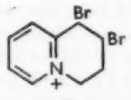


(XI)

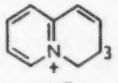


(XII)

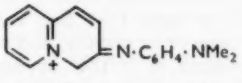
salt in its ultraviolet absorption, and is no doubt in fact the related dibromoiodide (XIV; X = IBr_2). The 3-methylene group in this would be expected to be reactive, and condensation with nitrosodimethylaniline was effected, giving the red-brown anil (XV).



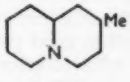
(XIII)



(XIV)



(XV)



(XVI)

Reduction of the dehydropyridocolinium and the 2-ethyl-3-methyldehydropyridocolinium ions with lithium aluminium hydride gave no definable product, but 2-methyldehydropyridocolinium iodide was hydrogenated over platinum oxide to octahydro-2-methylpyridocoline (XVI).

[6] Bradsher and Beavers, *J. Amer. Chem. Soc.*, 1955, **77**, 453.

Experimental

Difficulty was encountered in the analysis of many of the compounds described, which had often to be mixed with copper oxide to effect complete combustion.

4-Methyl-3-oxovaleraldehyde (*Case* 2).—A mixture of methyl *iso*propyl ketone (1 mol.) and ethyl formate (1 mol.) was added slowly to sodium wire (1 atom) under ether at 0°. After 48 hr. the pale yellow sodium salt was collected and the liberated *oxo-aldehyde* dried in ether (Na_2SO_4) and distilled. The unstable liquid, b. p. 54°/20 mm., gave a deep violet colour with ferric chloride (Found: C, 63·0; H, 7·9. $C_6H_{10}O_2$ requires C, 63·2; H, 8·8%).

Reactions with Ethyl Orthoformate.[12]—*Case* 1. Sodio-formylacetophenone (24 g.) was decomposed with acid and the free oxo-aldehyde, dried in ether (Na_2SO_4 and a little K_2CO_3), was used without further purification; ethyl orthoformate (20 g.), ethanol (20 ml.), and ferric chloride (0·5 g.) were added to the residue from evaporation of the ethereal solution, and the mixture was boiled for 10 min. The cooled solution was poured into cold aqueous sodium hydroxide and shaken with ether without delay; the ether layer was washed with alkali until a neutralised portion of the washings gave no colour with ferric chloride, washed with water, dried (Na_2SO_4), and distilled. The product (6·8 g.), b. p. 110—114°/0·04 mm., was probably a mixture of ethoxymethyleneacetophenone and formylacetophenone diethyl acetal (Found: C, 72·1; H, 7·4. Calc. for $C_{11}H_{12}O_2$: C, 75·0; H, 6·8. Calc. for $C_{13}H_{18}O_3$: C, 70·3; H, 8·1%). It decolorised bromine in carbon tetrachloride, afforded no dimedone derivative, and with alcoholic ferric chloride gave a colour only after some time. The same method was used in other cases (see Table 1), except nos. 1 and 8.

Table 1. *Initial and intermediate compounds.*

Case	Dicarbonyl compound	Intermediate (II)	B. p./mm.	Intermediate (III), b. p./mm.
1	Me·CO·CH_2·CHO	Acetal [7]	—	see exptl. part
2	Me_2CH·CO·CH_2·CHO	Mixture	90—112°/40	114—120°/0·5
3	Me_3C·CO·CH_2·CHO [8]	Mixture	92—96°/10	100—108°/0·05
4	Ph·CO·CH_2·CHO	Mixture	100—114°/0·04	*a*
5	Me·CO·CHMe·CHO [9]	Mixture	90—98°/10	100—112°/0·02
6	Me·CO·CH_2·COMe	Enol ether	74—78°/30 [b]	108—116°/0·5
7	Et·CO·CHMe·CHO	Mixture	92—96°/10	128—134°/0·2
8	Ph·CO·CH_2·COMe	Enol ether [10]	—	M. p. 78° [c]
9	Ph·CO·CHMe·CHO [11]	Mixture	100—106°/0·05	M. p. 62—63° [d]

[a] Could not be distilled; pale yellow after passage through alumina column. [b] Lit., b. p. 69—70°/10 mm. [c] Lemon-yellow needles of *4-ethoxy-2-phenyl-1-2′-pyridylpent-3-en-2-ol* (Found: C, 76·3; H, 7·6; N, 4·8. $C_{18}H_{21}O_2N$ requires C, 76·3; H, 7·4; N, 4·9%). [d] Colourless needles of *4-ethoxy-3-methyl-2-phenyl-1-2′-pyridylbut-3-en-2-ol* (Found: C, 76·7; H, 7·4; N, 4·9%).

Reactions with Picolyl-lithium.—*Case* 1. 4 : 4-Dimethoxybutan-2-one (25 g.) in ether (50 ml.) was added at 0° with stirring to ethereal 2-picolyl-lithium [13] from lithium (3 g.), bromobenzene (32 g.), and picoline (19 g.). After 1 hour's stirring at room temperature, ice was added and the organic material extracted with ether and dried (Na_2SO_4). Distillation afforded a golden-yellow oil (13·5 g.), b. p. 110—115°/0·2 mm., which darkened quickly in air. The diethyl acetal (4 g.) gave similarly a product (3·1 g.), b. p. 112—116°/0·15 mm. In the other cases a larger excess of picolyl-lithium was used, with otherwise the same procedure.

Ring-closure to Dehydropyridocolinium Salts.—The product (III) was boiled for a few minutes with ethanolic picric acid; in cases 1—7 (see Table 2) the dehydropyridocolinium picrate separated in good yield at once or on cooling, and crystallised from ethanol in yellow needles. In case 8 the product so obtained, m. p. 154°, appeared to be *4-oxo-2-phenyl-1-2′-picolylpentan-2-ol picrate* (IV) (Found: C, 54·6; H, 4·2; N, 12·1. $C_{22}H_{20}O_9N_4$ requires C, 54·6; H, 4·2; N, 11·6%); since it lost no weight at 78°/0·5 mm. in 6 hr., it was not a solvate. The picrate was refluxed for 10 min. with acetic anhydride containing a drop of sulphuric acid and poured into

[7] Royals and Brannock, *J. Amer. Chem. Soc.*, 1953, **75**, 2050.
[8] Couturier and Vignon, *Compt. rend.*, 1905, **140**, 1695.
[9] Benary, Meyer, and Charisius, *Ber.*, 1926, **59**, 108, 600.
[10] Claisen, *Ber.*, 1926, **59**, 144.
[11] Claisen and Meyerowitz, *Ber.*, 1889, **22**, 3277.
[12] Claisen, *Ber.*, 1907, **40**, 3903.
[13] Walter, *Org. Synth.*, 1943, **23**, 83.

water, the picrate (V) being obtained which, recrystallised from methanol, had the composition and properties recorded in Table 2.

Dehydropyridocolinium iodides were prepared by warming the same precursors with hydriodic acid (freshly distilled from red phosphorus); the solution was evaporated to dryness in a vacuum, the residue dissolved in hot ethanol and treated with sulphur dioxide to remove free iodine, and the solid which separated on cooling was crystallised from ethanol. 2-Methyldehydropyridocolinium iodide, pale yellow needles, had m. p. 136—138°, and with picric acid yielded the picrate identical with that prepared directly. 2 : 3-*Dimethyldehydropyridocolinium*

TABLE 2. *Dehydropyridocolinium picrates.*

	Substituents					Found (%)			Required (%)		
Case	2	3	4	M. p.	Formula	C	H	N	C	H	N
1	Me	—	—	161°	$C_{16}H_{13}O_7N_4$	51·8	3·7	14·8	51·6	3·3	15·1
2	Pr^i	—	—	156—167	$C_{18}H_{16}O_7N_4$	—	—	13·9	—	—	14·0
3	Bu^t	—	—	184	$C_{19}H_{18}O_7N_4$	54·8	4·3	13·6	55·1	4·3	13·5
4	Ph	—	—	171	$C_{21}H_{16}O_7N_4$	57·6	3·7	12·8	57·9	3·2	12·9
5	Me	Me	—	216 dec.	$C_{17}H_{14}O_7N_4$	52·7	3·9	14·3	52·9	3·6	14·5
6	Me	—	Me	150—151	,,	52·9	3·9	14·5	,,	,,	,,
7	Et	Me	—	189·5	$C_{18}H_{16}O_7N_4$	53·7	4·2	14·2	54·0	4·0	14·0
8	Ph	—	Me	226 dec.	$C_{22}H_{16}O_7N_4$	58·8	3·8	12·9	58·9	3·6	12·5

iodide, colourless plates, melted at 222—224° (dec.) (Found: N, 4·9. $C_{11}H_{12}NI$ requires N, 4·9%), and 2-*ethyl*-3-*methyldehydropyridocolinium iodide*, colourless needles, at 186—187° (Found: C, 48·6; H, 4·7; N, 4·5. $C_{12}H_{14}NI$ requires C, 48·2; H, 4·7; N, 4·7%).

In case 9, no dehydropyridocolinium salt could be obtained by treatment either with ethanolic picric acid or with mineral acid.

Pyridine-2-aldehyde Allylobromide.—Pyridine-2-aldehyde (2·2 g.) and allyl bromide (2·4 g.) were mixed and kept at room temperature for 4 weeks. The viscous, hygroscopic gum, which contained ionic bromine, slowly resinified when refluxed with 45% hydrobromic acid, rapidly with 50% sulphuric acid. Treatment with polyphosphoric acid at 100—120° for 12 hr. yielded, after dilution and neutralisation, only a little gummy picrate.

2-*Hydroxy*-4-*methyldehydropyridocolinium Picrate.*—Ethereal picolyl-lithium, prepared from lithium (1 g.), bromobenzene (12 g.), and 2-picoline (7 g.), was added to ethyl β-ethoxycrotonate [14] in ether so as to maintain gentle refluxing. 4-Ethoxy-1-2′-pyridylpent-3-en-2-one (VII), isolated as usual, was a dark oil, b. p. 126—132°/0·1 mm.; the *methiodide* had m. p. 126° after crystallisation from ethanol–ether (Found: C, 44·8; H, 5·3; N, 4·0; I, 36·5. $C_{13}H_{16}O_2NI$ requires C, 44·9; H, 5·2; N, 4·0; I, 36·6%). The base (VII) showed strong absorption bands at 1050—1060, 1111, and 1665 cm.$^{-1}$, in agreement with the assigned structure; the methiodide absorbed strongly at the first two frequencies, and also at 1630, 1658, and 3395 cm.$^{-1}$, suggesting enolisation of the ketomethylene system. With alcoholic picric acid, the base (VII) yielded a picrate, m. p. 136°, which gave a black gum on attempted recrystallisation; it appeared to be 2-*hydroxy*-4-*methyldehydropyridocolinium picrate* (VIII) (Found: C, 49·4; H, 3·5; N, 14·2. $C_{16}H_{12}O_8N_4$ requires C, 49·5; H, 3·1; N, 14·4%). Attempted reduction of the base (VII) by lithium aluminium hydride in ether, by aluminium *iso*propoxide in propan-2-ol–toluene, and by aluminium amalgam in moist ether, all gave unchanged ketone recognised as the picrate (VIII). Similar treatment left 2-acetonylpyridine [15] unchanged.

Reactions with Alkali.—Dehydropyridocolinium iodide was shaken with water and silver oxide for 15 min. No benzene-soluble material was obtained; the aqueous solution, which had pH 10, contained no iodide ions, precipitated silver oxide from silver nitrate solution, and with picric acid gave dehydropyridocolinium picrate. A concentrated aqueous solution of the same iodide gave no benzene-soluble product when warmed with excess of 10N-sodium hydroxide.

An aqueous solution of 3-phenyl-1 : 2-benzodehydropyridocolinium bromide, treated with silver oxide, gave no benzene-soluble material at once. The strongly alkaline aqueous filtrate (pH >10) yielded phenylbenzodehydropyridocolinium picrate with picric acid; when a portion was kept for 2 days, the solution, now neutral, had deposited brown, amorphous, benzene-soluble matter.

[14] Michael and Carlson, *J. Amer. Chem. Soc.*, 1935, **57**, 159.
[15] Beets, *Rec. Trav. chim.*, 1944, **63**, 120.

Addition of saturated potassium iodide solution to a hot aqueous solution of 2 : 3-benzodehydropyridocolinium bromide yielded the crystalline iodide. This, dissolved in water, was shaken with silver oxide under nitrogen for 15 min. and the undissolved organic material extracted with benzene, giving a neutral, halogen-free aqueous solution. The orange benzene extract, which darkened rapidly in air, yielded with picric acid benzodehydropyridocolinium picrate. An aqueous solution of the iodide gave with sodium hydroxide solution an orange precipitate, m. p. 80—83° after shrinking at 70°, which did not crystallise and with picric acid gave benzodehydropyridocolinium picrate.

Benzodehydropyridocolinium iodide (330 mg.) was mixed with nitromethane (100 mg.) and potassium hydroxide (150 mg.) in methanol, and the orange solution kept overnight. No condensation product could be isolated at this stage or after 1 hour's refluxing. No condensation was observed in similar experiments with 2 : 4-dinitrotoluene, acetone, acetophenone, diethyl malonate, or ethyl acetoacetate.

Addition of potassium ferricyanide (500 mg.) and potassium hydroxide (200 mg.) in water to aqueous dehydropyridocolinium iodide (180 mg.) gave a dark solution from which benzene extracted a small quantity of water-soluble solid, m. p. 70—75°, which gave an unstable picrate, m. p. 130—140°. The aqueous solution gave Prussian blue with ferric chloride. 3-Phenyl-1 : 2-benzodehydropyridocolinium bromide also reduced ferricyanide. 2 : 3-Benzodehydropyridocolinium iodide gave similarly a white amorphous precipitate, the filtrate from which contained ferrocyanide ion. The precipitate, which decomposed in air, and in hot solvents, may have been dimeric (*M*, cryoscopic in C_6H_6, 410).

Solutions of dehydropyridocolinium or 3-phenyl-1 : 2-benzodehydropyridocolinium salts with aqueous sodium cyanide gave no pseudo-cyanide even after long storage. With 2 : 3-benzodehydropyridocolinium iodide an unstable red precipitate was obtained; this dissolved in benzene and, when warmed with picric acid, gave benzodehydropyridocolinium picrate.

2-Methyldehydropyridocolinium iodide was refluxed in ethanol with *p*-dimethylaminobenzaldehyde (slight excess) and a drop of piperidine for 4—5 hr. The red solution deposited, on cooling, 2-p-*dimethylaminostyryldehydropyridocolinium iodide* (XI), claret-coloured needles, slightly soluble in water to a yellow solution; these had m. p. 316° after crystallisation from methanol (Found: C, 56·1; H, 4·9; N, 6·9. $C_{19}H_{19}N_2I$ requires C, 56·7; H, 4·7; N, 7·0%). A similar reaction with *p*-nitrosodimethylaniline gave dark brown needles, m. p. 230—232°, of *2-formyldehydropyridocolinium iodide* p-*dimethylaminoanil* (XII) (Found: C, 53·1; H, 4·3; N, 10·1. $C_{13}H_{18}N_3I$ requires C, 53·6; H, 4·5; N, 10·4%), slightly soluble in cold water to a cherry-red solution changed to pale yellow by hydrochloric acid.

Dibromoiodides.—The dehydropyridocolinium iodide in acetic acid was treated with a 10% solution of bromine in the same solvent, and the precipitate recrystallised from ethanol, giving the following *dibromoiodides*: *dehydropyridocolinium*, orange needles, m. p. 182—184° (Found: C, 25·9; H, 2·3; N, 3·9. $C_9H_8NIBr_2$ requires C, 25·9; H, 2·0; N, 3·4%); *2-methyldehydropyridocolinium*, orange plates and needles, m. p. 100—101° (Found: C, 27·6; H, 2·4; N, 3·3; Hal, 66·2. $C_{10}H_{10}NIBr_2$ requires C, 27·8; H, 2·3; N, 3·2; Hal, 66·6%); 2 : 3-*dimethyldehydropyridocolinium*, pale orange needles and plates, m. p. 160° (decomp.) (Found: C, 29·5; H, 2·9; N, 3·5. $C_{11}H_{12}NIBr_2$ requires C, 29·7; H, 2·7; N, 3·1%); *2-ethyl-3-methyldehydropyridocolinium*, yellow needles, m. p. 98° (Found: C, 31·8; H, 3·2; N, 3·4. $C_{12}H_{14}NIBr_2$ requires C, 31·4; H, 3·1; N, 3·1%); 2 : 3-*benzodehydropyridocolinium*, orange needles, m. p. 222—224° (Found: C, 33·5; H, 2·8; N, 3·1. $C_{13}H_{10}NIBr_2$ requires C, 33·4; H, 2·2; N, 3·0%). With iodine in ethanol, 2-ethyl-3-methyldehydropyridocolinium iodide gave the *tri-iodide*, m. p. 85° (Found: N, 2·4. $C_{12}H_{14}NI_3$ requires N, 2·5%).

3 : 4-Dihydrodehydropyridocolinium iodide gave the dibromide, m. p. 142°, as described by Boekelheide and Ross [1] for their presumed 1 : 2-dibromo-1 : 2 : 3 : 4-tetrahydropyridocolinium iodide (Found: C, 25·6; H, 2·6; N, 3·6. Calc. for $C_9H_{10}NIBr_2$: C, 25·8; H, 2·4; N, 3·4%). It showed absorption maxima at 211 (log ε 4·43) and 311 mμ (log ε 3·94), agreeing closely with the recorded figures for dihydrodehydropyridocolinium iodide and contrasting with those for tetrahydro-2-hydroxydehydropyridocolinium iodide.

3 : 4-*Dihydrodehydropyridocolinium tri-iodide*, prepared in and crystallised from ethanol, formed dark magenta plates, m. p. 133° (decomp.) (Found: C, 21·1; H, 2·2. $C_9H_{10}NI_3$ requires C, 21·1; H, 1·9%). The monoiodide (0·5 g.) was refluxed for 4 hr. in ethanol with *p*-nitrosodimethylaniline (0·3 g.) and a drop of piperidine. On concentration and cooling, the red solution deposited 3-p-*dimethylaminophenylimino*-3 : 4-*dihydrodehydropyridocolinium iodide*, red-brown

needles, m. p. 224—225° (decomp.) after crystallisation from ethanol (Found: C, 52·6; H, 4·9; N, 10·2. $C_{17}H_{18}N_3I$ requires C, 52·2; H, 4·6; N, 10·7%). The anil dissolved sparingly in water to a yellow solution, readily in acids to a colourless solution turned yellow by alkali.

Hydrogenation of Dehydropyridocolinium Iodide.—The iodide (140 mg.) in methanol rapidly absorbed 5 mols. of hydrogen over Adams catalyst (50 mg.). The product afforded a yellow picrate, needles (from ethanol), m. p. 150—151° (Found: C, 50·25; H, 5·8; N, 14·5. Calc. for $C_{16}H_{21}O_7N_4$: C, 50·4; H, 5·5; N, 14·7%). Clemo and Metcalfe [18] give 158° as the m. p. of octahydro-2-methylpyridocoline picrate prepared otherwise; the two products may differ stereochemically.

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THE UNIVERSITY, SHEFFIELD, 10. [*Received, April 18th*, 1958.]

[18] Clemo and Metcalfe, *J.*, 1937, 1518.

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624. *New Heteroaromatic Compounds. Part I. 9-Aza-10-boraphenanthrene.*

By M. J. S. DEWAR, VED P. KUBBA, and R. PETTIT.

Replacement of one carbon atom in an aromatic hydrocarbon by nitrogen gives rise to an isoconjugate positive ion; *e.g.*, the pyridinium ion is related in this way to benzene. Replacement by boron should give an analogous negative ion. Replacement of a pair of carbon atoms, one by nitrogen and one by boron, should therefore give a neutral aromatic system. Borazole is the only hitherto known compound of this type; we now describe a similar analogue of phenanthrene with the 9 : 10-carbon atoms so replaced. The parent compound, and derivatives with chlorine, hydroxy, methyl, ethyl, and phenyl attached to boron, have been prepared; they have the expected aromatic properties.

IF one carbon atom in an aromatic hydrocarbon is replaced by nitrogen, an isoconjugate positive ion is obtained; for example, the pyridinium ion $C_5NH_6^+$ is related in this way to benzene, C_6H_6. Replacement of one carbon atom by boron should likewise give rise to an isoconjugate negative ion, *e.g.*, $C_5BH_6^-$, but no compounds of this type are known. It follows that replacement of a pair of carbon atoms, one by nitrogen and one by boron, should give rise to a neutral aromatic system; thus three such molecules (I), (II), and (III) should be capable of existence, all isoconjugate with benzene. It has long been recognised that borazole (IV) is of this type, being derived from benzene by replacement of all three pairs of carbon atoms; the chemical and spectroscopic properties of borazole indicate that it is aromatic. However, no other such aromatic boron compounds have yet been prepared (unless boron nitride is regarded as such an analogue of graphite), and we have therefore undertaken a general study of this new class of aromatic system. In this preliminary paper we describe the preparation and properties of compounds derived from phenanthrene by replacing the 9-carbon atom by nitrogen and the 10-carbon atom by boron.

2-Aminodiphenyl with boron trichloride in hot benzene gave hydrogen chloride and a product which could not be purified but was probably 2-diphenylylaminoboron dichloride (V); this on heating with aluminium chloride gave in good yield a compound $C_{12}H_9BNCl$ which, for reasons given below, we believe to be 10-chloro-9-aza-10-boraphenanthrene (VI; R = Cl).

The chloro-compound was hydrolysed with extreme ease, even when kept in air for a day, to the corresponding hydroxide (VI; R = OH), which was unchanged by prolonged boiling with alkali; this indicates that the boron atom must be attached to carbon, since the B–N bond is readily broken by alkaline hydrolysis. Reduction of the chloro-compound

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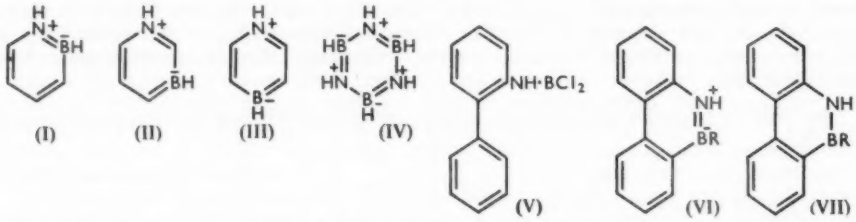
by lithium aluminium hydride gave the parent substance (VI; R = H); this was quite stable and its spectrum (Fig. 1) resembled that of phenanthrene. The mode of formation of these compounds, their spectral resemblance to phenanthrene, and their stability, leave little doubt that they are indeed derivatives of 9-aza-10-boraphenanthrene (VI; R = H),



and are therefore representatives of a new class of aromatic compound. The spectra of the hydroxide in neutral and alkaline conditions (Fig. 2) are very similar, and quite different from those of simple diphenyl derivatives; the B–N bond is therefore clearly much

FIG. 1. *Ultraviolet spectra of* 9-*aza*-10-*boraphenanthrene* (——), *and phenanthrene* (– – –).

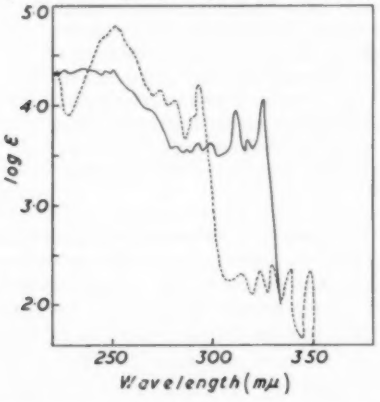
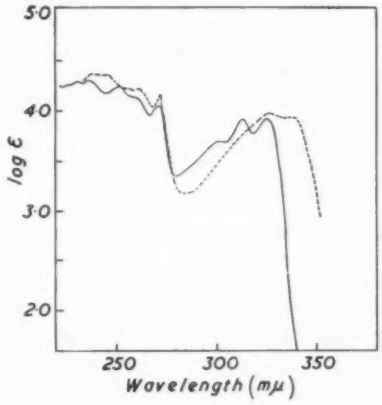


FIG. 2. *Ultraviolet spectra of* 10-*hydroxy*-9-*aza*-10-*boraphenanthrene in* cyclohexane *or alcohol* (——), *and* 10% *aqueous alkali* (– – –).



stronger than it is in simple amides of boric acid, implying that the compounds behave as aromatic analogues of phenanthrene (VI) rather than as cyclic boron amides * (VII). The stability of the parent compound (VI; R = H), a boron hydride, also supports this formulation.

Confirmation of these structures has been provided by two independent syntheses of 10-phenyl-9-aza-10-boraphenanthrene (VI; R = Ph). This could be obtained either by a Grignard reaction between the chloro-compound (VI; R = Cl) and phenylmagnesium bromide, or by condensing 2-aminodiphenyl with phenylboron dichloride in presence of aluminium chloride. The methyl and the ethyl analogue (VI; R = Me and Et) were also prepared by Grignard reactions from the chloro-compound (VI; R = Cl). The spectra of all these derivatives (VI) were very similar (cf. Table and Fig. 1).

The spectrum of 9-aza-10-boraphenanthrene (VI; R = H) itself is interesting (Fig. 1). It resembles very closely that of phenanthrene in the position of the main absorption bands, but the intensity of the α-band (275 mμ region) is very much greater. This would

* Of course the compounds are mesomeric, (VI) and (VII) being contributing structures; writing them as (VI) is intended to emphasise their aromatic nature.

be expected on the basis of a theory of hydrocarbon spectra proposed by Dewar and Longuet-Higgins [1] and by Moffitt.[2] According to these authors the α- and the β-band of alternant hydrocarbons arise from the second and the third transition respectively which are degenerate in simple molecular-orbital theory; configuration interaction splits the degenerate excited states into a lower and an upper one. Transition to the lower level from the ground state is forbidden, corresponding to the weak α-band. Introduction of

Ultraviolet absorption spectra of 10-*substituted* 9-*aza*-10-*boraphenanthrenes: wavelengths* (mμ) *and, in parentheses,* $\log_{10} \varepsilon$.

10-Methyl-9-aza-10-boraphenanthrene

$\lambda_{max.}$	220(4·203), 224(4·195), 230(4·191), 236(4·191), 240(4·203), 246(4·211), 250(4·205), 298(3·725), 312(3·944), 324(3·995)
$\lambda_{min.}$	222(4·167), 228(4·171), 234(4·178), 238(4·188), 244(4·191), 248(4·198), 280(3·496), 304(3·612), 318(3·694), 334(2·413)

10-Ethyl-9-aza-10-boraphenanthrene

$\lambda_{max.}$	220(4·332), 230(4·295), 238(4·312), 250(4·325), 298(3·747), 313(3·928), 325(4·046)
$\lambda_{min.}$	222(4·243), 234(4·286), 242(4·286), 280(3·520), 303(3·625), 319(3·698), 336(2·073)

10-Phenyl-9-aza-10-boraphenanthrene

$\lambda_{max.}$	224(4·320), 238(4·350), 256(4·389), 300(3·789), 314(3·964), 328(4·047)
$\lambda_{min.}$	220(4·300), 226(4·316), 240(4·342), 281(3·653), 308(3·690), 322(3·750), 340(2·300)

heteroatoms into an alternant hydrocarbon should have no first-order effect on the wavelengths of the absorption bands [3] but should remove the degeneracy to which the weakness of the α-bands is due. This effect is well known for simple nitrogen heterocycles; for example, introduction of nitrogen atoms into naphthalene gives rise to compounds (quinoline, quinazoline, etc.) in which the positions of the main absorption bands change little, but in which the intensity of the α-band is greatly increased.

Experimental

Some analyses for elements other than boron were kindly carried out by the microanalytical laboratory of the Imperial College of Science and Technology, London; boron was determined by the volumetric method developed by Leigh, Fowler, and Kraus.[4] M. p.s are corrected. Molecular weights were determined by freezing-point depression of camphor.

10-*Chloro*-9-*aza*-10-*boraphenanthrene*.—A solution of boron trichloride (12 g.) in benzene (50 ml.) was added slowly to one of 2-aminodiphenyl (17·4 g.) in benzene (350 ml.), and the mixture then boiled under reflux for 10 hr. The benzene was distilled off under reduced pressure, leaving crystalline 2-diphenylaminoboron dichloride (15 g.). This crude dichloride (6 g.) was heated with aluminium chloride (0·5 g.) to 175° for 7 hr. The resulting 10-*chloro*-9-*aza*-10-*boraphenanthrene* sublimed at 160—70°/0·05 mm., forming needles (2·8 g., 55%), m. p. 93—94° (Found: C, 67·7; H, 4·3; N, 6·8; Cl, 15·0. $C_{12}H_9NClB$ requires C, 67·5; H, 4·2; N, 6·6; Cl, 16·6%) (Repeated chlorine analyses showed a wide variation between 0·5% and 15·0%, clearly due to atmospheric hydrolysis. The figure quoted was the highest value, obtained when the analyst had been warned to take special precautions. Partial hydrolysis is also indicated by the fact that the analyses for C, H, and N are all slightly high, whereas carbon analyses on boron compounds are usually low.)

10-*Hydroxy*-9-*aza*-10-*boraphenanthrene*.—The chloro-compound, on storage in air for 24 hr., on crystallisation from moist light petroleum (b. p. 60—80°), or on treatment with water, gave almost theoretical yields of 10-*hydroxy*-9-*aza*-10-*boraphenanthrene*, which crystallised from light petroleum (b. p. 60—80°) in colourless needles, m. p. 169—170° (Found: C, 73·5; H, 5·5; N, 7·2; B, 5·6. $C_{12}H_{10}ONB$ requires C, 73·9; H, 5·1; N, 7·2; B, 5·6%). Its *picrate* was prepared from benzene solution, as orange crystals, m. p. 158—160° (Found: C, 50·8; H, 3·2; N, 13·3. $C_{18}H_{13}O_8N_4B$ requires C, 50·9; H, 3·1; N, 13·2%).

9-*Aza*-10-*boraphenanthrene*.—A solution of lithium aluminium hydride (0·8 g.) in dry ether

[1] Dewar and Longuet-Higgins, *Proc. Phys. Soc.*, 1954, **67**, 795.
[2] Moffitt, *J. Chem. Phys.*, 1954, **22**, 1820.
[3] Dewar, *J.*, 1950, 2329.
[4] Leigh, Fowler, and Kraus, *J. Amer. Chem. Soc.*, 1940, **62**, 1143.

(100 ml.) was added slowly with stirring and cooling (ice) to a solution of crude 10-chloro-9-aza-10-boraphenanthrene (12 g.) in dry ether (200 ml.), and the whole then boiled for 1 hr. Ethyl acetate (10 ml.) was added and the solution was then filtered and evaporated to dryness. The residue crystallised from light petroleum (b. p. 40—60°), giving 9-*aza*-10-*boraphenanthrene* (7 g., 70%) as colourless plates, m. p. 69—70° (Found: C, 80·0; H, 5·6; N, 7·8; B, 5·9%; *M*, 180. $C_{12}H_{10}NB$ requires C, 80·5; H, 5·6; N, 7·8; B, 6·0%; *M*, 179).

10-*Phenyl*-9-*aza*-10-*boraphenanthrene*.—(a) *From phenylboron dichloride*. Phenylboron dichloride [5] (4·5 g.) and 2-aminodiphenyl (5 g.) in benzene (400 ml.) were boiled for 8 hr., then evaporated to dryness under reduced pressure. The residue was heated with anhydrous aluminium chloride (0·5 g.) for 15 hr. at 170—180°, cooled, and crystallised first from benzene and then from light petroleum (b. p. 40—60°), giving 10-*phenyl*-9-*aza*-10-*boraphenanthrene* as light brown prisms (4·0 g., 66%), m. p. 110—111·5° (Found: C, 84·5; H, 5·4; N, 5·7; B, 4·1. $C_{18}H_{14}NB$ requires C, 84·8; H, 5·5; N, 5·5; B, 4·2%). (b) *By a Grignard reaction*. To a solution of crude 10-chloro-9-aza-10-boraphenanthrene (10 g.) in dry benzene (75 ml.) was added slowly a solution of phenylmagnesium bromide prepared from magnesium (1·1 g.) and bromobenzene (7 g.), and the solution then boiled under reflux for ¾ hr. Water was added and the benzene layer separated, dried, and evaporated; the residue after recrystallisation from light petroleum had m. p. and mixed m. p. 110° (6·9 g., 59%).

10-*Methyl*-9-*aza*-10-*boraphenanthrene*.—Prepared by a Grignard reaction in the same way as the phenyl analogue, in 67% yield, 10-*methyl*-9-*aza*-10-*boraphenanthrene* crystallised from ethanol in colourless needles, m. p. 103—104° (Found: C, 80·7; H, 6·4; N, 7·2; B, 5·4. $C_{13}H_{12}NB$ requires C, 80·9; H, 6·2; N, 7·3; B, 5·6%).

10-*Ethyl*-9-*aza*-10-*boraphenanthrene*.—Prepared in the same way, in 72% yield, 10-*ethyl*-9-*aza*-10-*boraphenanthrene* crystallised from ethanol in colourless needles, m. p. 77—78° (Found: C, 80·8; H, 6·7; N, 7·0; B, 5·2. $C_{14}H_{14}NB$ requires C, 81·2; H, 6·8; N, 6·8; B, 5·2%).

Spectroscopic Data.—The spectra were determined for *cyclo*hexane solutions by using a Unicam S.P. 500 spectrophotometer.

We thank the University of London for the award of an I.C.I. Research Fellowship (to R. P.), and for a grant for the purchase of apparatus.

QUEEN MARY COLLEGE, (UNIVERSITY OF LONDON),
MILE END ROAD, LONDON, E.1.
[Present address (R. P.): UNIVERSITY OF TEXAS,
AUSTIN 12, TEXAS, U.S.A.]

[*Received, December 23rd*, 1957.]

[5] Abel, Dandegaonker, Gerrard, and Lappert, *J.*, 1956, 4697.

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625. *New Heteroaromatic Compounds. Part II.*[1] *Boron Compounds Isoconjugate with Indole, 2 : 3-Benzofuran, and Thionaphthen.*

By M. J. S. DEWAR, VED P. KUBBA, and R. PETTIT.

Boron analogues of three aromatic compounds containing five-membered rings have been prepared. Their ultraviolet spectra indicate varying degrees of aromatic behaviour; the spectrum of 2-phenylbenzo-1 : 3-diaza-2-borole (I) resembles that of 2-phenylbenziminazole very closely, indicating that (I) has a similar aromatic system of π-electrons; that of the dioxaborole (II) differs little from that of catechol.

IN the preceding paper [1] we pointed out that a wide range of new heteroaromatic systems should exist, derived from normal aromatic compounds by replacing pairs of carbon atoms, one by boron and one by nitrogen. We there recorded 9-aza-10-boraphenanthrene (the second known compound of this type) whose stability and ultraviolet spectrum indicated that it was isoconjugate with phenanthrene. We now report compounds containing boron atoms in five-membered rings, isoconjugate with indole, 2 : 3-benzofuran, and thionaphthen.

[1] Part I, preceding paper.

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Our compounds were obtained by heating a solution of an appropriate *ortho*-disubstituted benzene derivative in benzene with phenylboron dichloride, hydrogen chloride being evolved. The yields were good, except in the case of the benzofuran analogue (III); the reaction of *o*-phenylenediamine with phenylboron dichloride led to extensive polymerisation. Addition of triethylamine to assist in the elimination of hydrogen chloride seemed

FIG. 1. *Ultraviolet spectra of 2-phenylbenzo-1 : 3-diaza-2-borole* (—), *2-phenylbenziminazole* (. . .) *and o-phenylenediamine* (– – –).

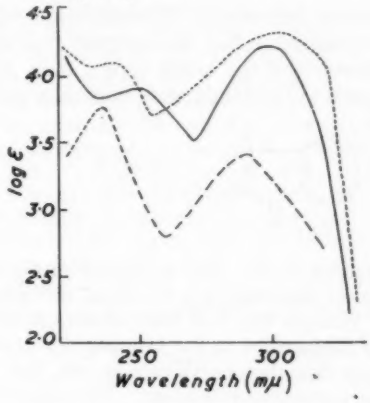


FIG. 2. *Ultraviolet spectra of 2-phenylbenzo-1 : 3 : 2-dioxaborole* (. . .), *catechol* (— · — · —), *2-phenylbenzo-1 : 3 : 2-dithiaborole* (——) *and dithiocatechol* (– – –).

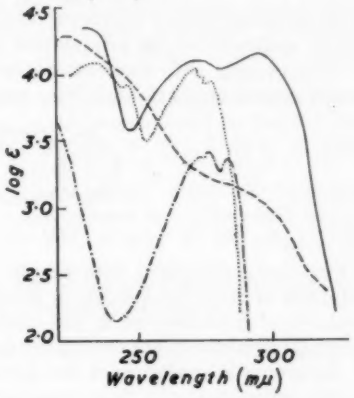


FIG. 3. *Ultraviolet spectra of 2-phenylbenzo-1 : 3 : 2-thiazaborole* (——), *2-phenylbenzothiazole* (. . .), *and o-aminothiophenol* (– – –).

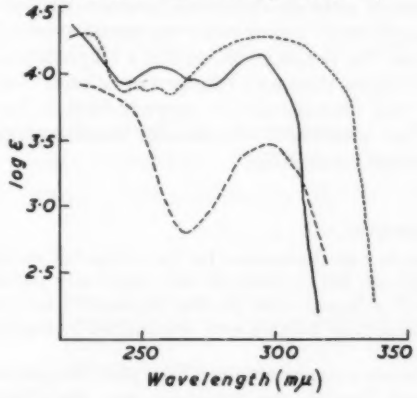
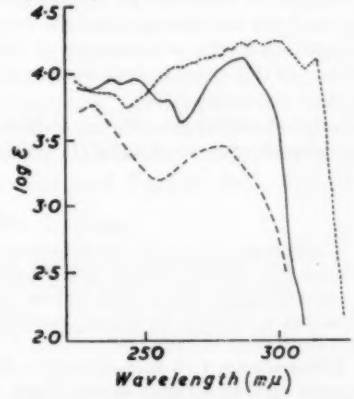


FIG. 4. *Ultraviolet spectra of 2-phenylbenzo-1 : 3 : 2-oxazaborole* (——), *2-phenylbenzoxazole* (. . .), *and o-aminophenol* (– – –).



to have little effect. These compounds are all crystalline, and soluble in benzene, ether, and chloroform. *o*-Phenylenediamine gave 2-phenylbenzo-1 : 3-diaza-2-borole (I), and catechol gave the corresponding dioxaborole (II). Analogous reactions of *o*-aminophenol, dithiocatechol, and *o*-aminothiophenol gave the corresponding oxa-azaborole (III), dithiaborole (IV), and thia-azaborole (IV). The structures of these compounds follow from their method of preparation, elementary analysis, and molecular-weight determination; moreover they were all hydrolysed by acid to the parent *ortho*-disubstituted benzene derivative and phenylboronic acid.

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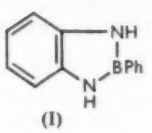
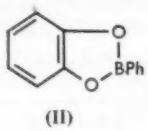
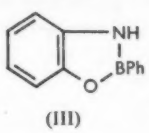
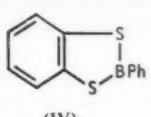
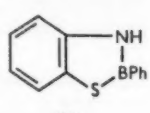
The ultraviolet spectra, together with those of various reference substances, are shown in Figs. 1—4. Those of compounds (I), (III), and (V) resemble closely those of 2-phenylbenziminazole, 2-phenylbenzoxazole, and 2-phenylbenzothiazole respectively, and differ


(I)

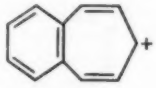

(II)

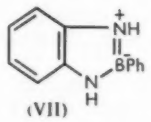

(III)


(IV)


(V)

markedly from those of the parent disubstituted benzene derivatives. This not only provides further evidence for the formulation of the boron compounds but also suggests that they are isoconjugate with conventional aromatic compounds of the indole type. If so, they should exhibit aromatic stability; compounds (I) and (V) certainly seem unusually stable


(VI)


(VII)

to hydrolysis, compared with simple amides of boronic acids. We are investigating the stabilities of these compounds in detail. A structure determination by *X*-ray diffraction would be of great interest in this connection; for example the B–N bond lengths in compound (I) would indicate clearly the importance of conjugation in the five-membered ring.

No aromatic analogues of the dioxaborole (II) or dithiaborole (IV) are known, but the spectra differ markedly from those of catechol or *o*-dimercaptobenzene. The difference is particularly marked in the case of compound (IV), probably because it can be regarded as a hetero-analogue of benzotropylium (VI) (the formula of which has been written in such a way as to emphasise the resemblance). Examination of Figs. 1—4 suggests that the difference between the boroles and the parent *ortho*-disubstituted benzene derivatives is greater for the nitrogen and the sulphur compounds; this is what one would expect, for conjugation leads to a transfer of charge from the heteroatoms in the 1 : 3-positions to boron and this should occur less readily with oxygen than with nitrogen or sulphur (which are less electronegative). The spectrum of the diazaborole (I) suggests that it has a structure closely approximating to that of the corresponding benziminazole; this resemblance can be emphasised by writing (I) in the zwitterionic form (VII).

Experimental

The boron analyses for the following compounds were determined by the volumetric method developed by Leigh, Fowler, and Kraus.[2] Although the compounds were rigorously purified by crystallisation, the carbon values were rarely obtained with as close agreement with the calculated as is usual for organic compounds. Molecular weights were determined by freezing-point depression of camphor.

2-Phenylbenzo-1 : 3-diaza-2-borole.—Phenylboronic acid was obtained from phenylmagnesium bromide and tri-*n*-butyl borate[3] and converted through the anhydride into phenylboron dichloride.[4]

Phenylboron dichloride (4·0 g.) in dry benzene (50 ml.) was added dropwise and with constant stirring to *o*-phenylenediamine (3·0 g.) in dry benzene (350 ml.) at room temperature, moisture being excluded. The mixture was then boiled under reflux with stirring until evolution of hydrogen chloride had ceased (8 hr.), cooled, filtered, and evaporated under reduced pressure. The brown crystalline residue (1·8 g.) of *2-phenylbenzo-1 : 3-diaza-2-borole* crystallised from

[2] Leigh, Fowler, and Kraus, *J. Amer. Chem. Soc.*, 1940, **62**, 1143.
[3] Bean and Johnson, *ibid.*, 1932, **54**, 4415.
[4] Abel, Dandegaonker, Gerrard, and Lappert, *J.*, 1956, 4697.

benzene or light petroleum (b. p. 60—80°) in white plates, m. p. 204—206° (Found: C, 73·9; H, 5·9; N, 14·3; B, 5·6%; *M*, 188. $C_{12}H_{11}N_2B$ requires C, 74·3; H, 5·7; N, 14·4; B, 5·6%; *M*, 194). When warmed with mineral acids or sodium hydroxide solution it gave phenylboronic acid and *o*-phenylenediamine.

2-*Phenylbenzo*-1 : 3-*dioxa*-2-*borole*.—Phenylboron dichloride (5 g.) in dry benzene (50 ml.) was added dropwise to catechol (3·5 g.) in benzene (600 ml.) and the mixture stirred under reflux for 6 hr. The benzene was then distilled off, leaving a quantitative yield of 2-*phenylbenzo*-1 : 3-*dioxa*-2-*borole*, which formed white plates, m. p. 109—110°, from benzene or light petroleum (Found: C, 73·0; H, 4·7; B, 5·5. $C_{12}H_9O_2B$ requires C, 73·5; H, 4·6; B, 5·5%).

2-*Phenylbenzo*-1 : 3-*dithia*-2-*borole*.—This compound was prepared in excellent yield in the usual way from dithiocatechol and phenylboron dichloride (7 hours' refluxing were required and no polymeric material was formed). The *dithiaborole* crystallised from light petroleum in white plates, m. p. 130—131° (Found: C, 61·3; H, 3·7; B, 5·1; S, 27·5. $C_{12}H_9S_2B$ requires C, 63·1; H, 3·9; B, 4·8; S, 28·1%).

2-*Phenylbenzo*-1 : 3-*thiaza*-2-*borole*.—Prepared as above from *o*-aminothiophenol and phenylboron dichloride the *thiazaborole* formed white needles (which after several recrystallisations from dry benzene had m. p. 154—156°) (Found: C, 68·3; H, 4·7; N, 6·7; S, 15·1; B, 5·0%; *M*, 220. $C_{12}H_{10}NSB$ requires C, 68·3; H, 4·7; N, 6·6; S, 15·2; B, 5·1%; *M*, 211).

2-*Phenylbenzo*-1-*oxa*-3-*aza*-2-*borole*.—Prepared (with a small amount of polymer) by heating *o*-aminophenol and phenylboron dichloride as before, the *oxa-azaborole* crystallised from benzene in white plates, m. p. 105—106° (Found: C, 72·1; H, 4·8; N, 6·9; B, 5·3. $C_{12}H_{10}ONB$ requires C, 73·9; H, 5·1; N, 7·2; B, 5·5%).

Spectra.—For the determination of their spectra 2-phenylbenziminazole,[5] 2-phenylbenzoxazole,[6] and 2-phenylbenzothiazole [7] were prepared by established procedures.

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Queen Mary College, (University of London),
Mile End Road, London, E.1.
[Present address (R. P.): University of Texas,
Austin 12, Texas, U.S.A.]

[*Received, December 23rd*, 1957.]

[5] Jerchel, Fisher, and Kracht, *Annalen*, 1952, **575**, 162.
[6] Desai, Hunter, and Khalidi, *J.*, 1934, 1186.
[7] Bogert and Snell, *J. Amer. Chem. Soc.*, 1924, **46**, 1308.

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626. *Electrophilic Substitution. Part XII.* The Nitration of Diphenylmethane, Fluorene, Diphenyl Ether, Dibenzofuran, Diphenylamine, and Carbazole; Relative Reactivities and Partial Rate Factors.*

By M. J. S. Dewar and D. S. Urch.

The nitrations mentioned in the title, carried out in acetic anhydride, have been studied quantitatively. The proportions of isomers and relative overall reactivites have been determined and partial rate factors calculated. Dibenzofuran is less reactive than diphenyl ether, and carbazole than diphenylamine.

The purpose of this series of papers is to test the molecular-orbital theory of chemical reactivity, in particular the simplified version put forward [1] by one of us some years ago. Previous investigations have dealt with the nitration of alternant aromatic hydrocarbons [2] and heterocycles; [3] here we report preliminary work on the effect of $-E$ substituents and of ring-closure to non-alternant systems. In these cases the simple molecular-orbital

* Part XI, *J.*, 1957, 2521.

[1] Dewar, *J. Amer. Chem. Soc.*, 1952, **74**, 3341, 3345, 3350, 3353, 3355, 3357.
[2] Dewar, Mole, and Warford, *J.*, 1956, 3581.
[3] Dewar and Maitlis, *J.*, 1957, 2521.

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treatment [1] is not so applicable, and more elaborate theoretical methods must be used; the results of such a treatment will be reported in a later paper.

The compounds studied were diphenylmethane, fluorene, diphenyl ether, dibenzofuran, diphenylamine, and carbazole. They were first nitrated individually in acetic anhydride, and the proportions of isomers in the product were estimated spectrophotometrically by the method previously described.[4] The conditions were chosen to lead almost exclusively to mononitro-compounds and the estimations of isomers in most cases were accurate within ±1%. The individual compounds are discussed below. Our results are summarised in Table 1.

Diphenylmethane.—It has been reported [5] that nitration of diphenylmethane with cold fuming nitric acid yields 2 : 4′- and 4 : 4′-dinitrodiphenylmethane. By using an excess of hydrocarbon with nitric acid–acetic anhydride we were able to obtain mainly a mixture of mononitro-derivatives. Since the spectra of these are similar, and since a little benzophenone was also formed, the error in estimating the proportions of isomers was larger (±10%) than usual.

Fluorene.—Nitration of fluorene in acetic acid with an excess of fuming nitric acid gives 2 : 5- and 2 : 7-dinitrofluorene,[6] suggesting that the 2- and the 4-position have comparable reactivites; Weissberger [7] has indeed isolated 4-nitrofluorene in preparation of 2-nitrofluorene. We found both isomers in the nitration product and some indication that the 3-isomer was also present; however, the amount of the latter (2%) was not much greater than our estimated experimental error (±1%).

Diphenyl Ether.—Suter [8] reported that nitration of diphenyl ether gives the *p*- and the *o*-nitro-derivative in the ratio 1·2 : 1; this agrees with our value (1 : 1).

Dibenzofuran.—The isomer distribution has already been reported.[9]

Diphenylamine.—Ryan and Ryan,[10] who studied the nitration of diphenylamine in a variety of solvents, reported that nitration in acetic acid took place only in presence of an excess of nitric acid and gave a green solution, presumably implying that the diphenylaminium ion-radical was formed to some extent.[11] The products isolated were 2 : 2′- and 2 : 4′-dinitrodiphenylamine together with some *N*-nitrosodiphenylamine. We have been able to obtain a mixture of 2- and 4-nitrodiphenylamine as the main nitration product by using an excess of diphenylamine in acetic anhydride; *N*-acetyldiphenylamine was also formed, together with *N*-acetyl-2- and -4-nitrodiphenylamine. Since *N*-acetyldiphenylamine was not significantly attacked under our conditions we assumed that the by-products arose from acetylation of *N*-nitrodiphenylamines; the proportions of isomers given in Table 1, therefore, refer to the combined yields of nitro-compounds and their acetyl derivatives.

Carbazole.—Nitration of carbazole in acetic acid has been reported [12] to give mainly 3-nitrocarbazole, together with about 5% of the 1-isomer; we found that the product contained much more than 5% of the 1-isomer, and there were indications that a little 2-nitrocarbazole had also been formed (cf. fluorene).

The relative overall reactivities of the compounds were then determined by the competitive method. Each mixture of mononitro-compounds was analysed spectrophotometrically,[4] the proportions of isomers being assumed to be the same as in the products of the simple nitrations. This enabled us to treat the product from each competitive nitration as a binary mixture. Diphenylmethane and dibenzofuran were compared with

[4] Dewar and Urch, *J.*, 1957, 345.
[5] Staedel, *Annalen*, 1878, **194**, 363.
[6] Morgan and Thomason, *J.*, 1926, 2691; Anantakrishnan and Hughes, *J.*, 1935, 1607; Courtot, *Ann. Chim.* (*France*), 1930, **14**, 5.
[7] Weissberger, personal communication.
[8] Suter, *J. Amer. Chem. Soc.*, 1929, **51**, 2583.
[9] Dewar and Urch, *J.*, 1957, 345.
[10] Ryan and Ryan, *Proc. Roy. Irish Acad.*, 1917—19, *B*, **34**, 195, 198, 213.
[11] Cf. Jones and Culbertson, *Proc. Iowa Acad. Sci.*, 1942, **49**, 287.
[12] Morgan and Mitchell, *J.*, 1931, 3283; Lindemann, *Ber.*, 1924, **57**, 555.

diphenyl, and carbazole with perylene; the reactivities of diphenyl and perylene at 25° relative to benzene are known.[2] Diphenyl ether was compared with dibenzofuran, diphenylamine with carbazole, and fluorene with diphenyl ether. In this way we obtained the relative overall reactivities (benzene = 6) given in the first column of Table 2; and

TABLE 1. *Proportions of isomers in mononitro-derivatives formed by nitration in acetic anhydride at 0° and 25°.*

	At 0°				At 25°			
Isomer:	1	2	3	4	1	2	3	4
Diphenylmethane	—	52	—	48	—	38	—	62
Fluorene	—	63	3	34	—	69	2	29
Diphenyl ether	—	51	—	49	—	50	—	50
Dibenzofuran [8]	25	39	36	—	19	40	41	—
Diphenylamine	—	76	—	24	—	71	—	29
Carbazole	29	1	70	—	28	2	70	—

these together with the isomer ratios of Table 1 led to the partial rate factors (corrected for statistical factors) shown in the remaining columns of Table 2. The errors in these are uncertain; in the analogous work on hydrocarbons [2] it appeared that the values obtained were not in error by more than 50%.

TABLE 2. *Overall reactivities and partial rate factors for nitration in acetic anhydride at 25°.*

Compound	Overall reactivity ($C_6H_6 = 6$)	Partial rate factors for position 1	2	3	4
Diphenylmethane	117	—	13	—	32
Fluorene	608	—	2040	60	944
Diphenyl ether	936	—	117	—	23
Dibenzofuran	470	47	94	94	—
Diphenylamine	4,430,000	—	831,000	—	575,000
Carbazole	222,000	32,100	1100	77,600	—

Molecular-orbital treatment of these reactions will be described in a later paper; attention may be drawn to the comparisons diphenyl ether–dibenzofuran and diphenylamine–carbazole, which indicate that closure of the five-membered ring in each case lowers the overall reactivity.

EXPERIMENTAL

Materials.—Chromatography was carried out with Peter Spence's alumina (type "H", 100/200 mesh). Solvents were distilled before use. Fluorene was purified by chromatography from light petroleum (b. p. 40—60°) on alumina, and had m. p. 117—117·5°. Perylene was prepared by decarboxylation of perylenetetracarboxylic acid and purified by recrystallisation to m. p. 271—272°. Carbazole was prepared by dehydrogenation [13] of tetrahydrocarbazole and purified by chromatography from benzene on alumina; it had m. p. 244—245°. Nitric acid (*d* 1·5), acetic anhydride, diphenyl, diphenyl ether, diphenylmethane, and dibenzofuran were commercial specimens, used without further purification. The preparation and spectra (in 95% EtOH) of reference compounds are listed in Table 3.

3-Nitrofluorene was not prepared; the spectrum reported by Hayashi and Nakayama [21] was used in the analysis. Likewise we used for 4-nitrofluorene the spectrum reported by Weissburger and Weissburger.[22]

The preparation of 1- and 3-nitrocarbazole presented special features. 3-Nitrocarbazole was prepared by Lindemann's method [23] and purified by recrystallisation six times from acetic acid, and then five times from ethanol; it then formed yellow crystals, m. p. 215·5—216·5°.

[13] Gabriel and Stelzner, *Ber.*, 1896, **29**, 1303.

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Slow crystallisation from benzene gave a dark wine-red allotropic form, m. p. 213—215°, converted into the yellow form by recrystallisation from ethanol. Both forms had identical ultraviolet spectra. 1-Nitrocarbazole was isolated from the mother-liquors from the first recrystallisation of the 3-isomer; after it had been chromatographed three times from benzene on alumina it formed bright yellow needles, m. p. 186—187°.

TABLE 3. *Spectra of reference compounds, and references to methods of preparation.*

Compound	Ref.	M. p.	Spectrum in 95% ethanol (except where stated) $\lambda_{max.}$ (mμ) ($\log_{10}\varepsilon$)	$\lambda_{min.}$ (mμ) ($\log_{10}\varepsilon$)
2-Nitrodiphenylmethane	13	Oil	254(3·663)	238(3·580)
3-Nitrodiphenylmethane	14	Oil	264(3·881)	236(3·574)
4-Nitrodiphenylmethane	15	30—31°	278(4·020)	234(3·465)
2-Nitrofluorene	16	155—156	332(4·254), 234(3·980)	265(3·202), 222(3·920)
2-Nitrodiphenylamine	17	75·5—76	428(3·820), 259(4·150), 220(4·125), shoulder at 282(4·05)	325(2·631), 238(4·016), 214(4·107)
3-Nitrodiphenylamine	17	113—114	367(3·167), 282(4·209), 265(4·258) (in light petroleum, b. p. 40—60°)	320(2·718), 278(4·205)
4-Nitrodiphenylamine	17	132·5—133	391(4·293), 258(3·978), 228(3·818)	308(3·156), 234(3·807), 222(3·811)
N-Acetyl-2-nitrodiphenylamine	18	135—136	234(4·237), shoulders at 308(3·184), 266(3·671)	218(4·147)
N-Acetyl-3-nitrodiphenylamine	18	66—66·5	317(3·117), 244(4·318) (in light petroleum, b. p. 40—60°)	300(3·046), 220(3·990)
N-Acetyl-4-nitrodiphenylamine	18	100—101	310(3·981), 228(4·091)	262(3·609), 218(4·081)
N-Acetyldiphenylamine	18	101—102	236(4·041)	222(3·954)
2-Nitrodiphenyl ether	19	Oil	313(3·337)	286(3·253)
4-Nitrodiphenyl ether	19	31—31·5°	303(4·088)	250(3·420)
1-Nitrocarbazole	See below	186—187	403(3·855), 301(4·127), 260(3·957), 222(4·682)	316(3·239), 281(3·814), 256(3·944)
2-Nitrocarbazole	20	165—60	340(4·151), 281(3·867), 250(4·353), 212(4·362), shoulders at 259(4·290), 241(4·250), 222(4·104)	300(3·640), 271(3·792), 228(4·029)
3-Nitrocarbazole	See below	See below	366(3·985), 308(4·130), 279(4·374), 231(4·451), shoulder at 270(4·180)	330(3·777), 289(3·987), 254(3·640), 218(4·296)
4-Nitrocarbazole	20	181—20	361(3·765), 222(4·698), shoulder at 290(3·757)	312(3·364)

Nitrations.—A weighed amount of substance was dissolved in acetic anhydride (300 c.c.). The required amount of nitric acid (*d* 1·5) in acetic anhydride (50 c.c.) was added, and the flask containing the nitric acid solution rinsed into the reaction mixture with acetic anhydride (50 c.c.). All the solutions had previously been brought to the required temperature (0° or 25°) in an ice-bath or thermostat. After a suitable period the solution (usually yellow) was poured with stirring into ice-water (1 l.). When hydrolysis was complete, the organic material was isolated with chloroform and chromatographed on an alumina column (20 × 4 cm.). After excess of starting material had been eluted with light petroleum, the nitro-compounds were eluted with ether and rechromatographed 3—6 times. The combined fractions of starting material were evaporated, weighed, and analysed by ultraviolet spectrophotometry;[4] the combined nitro-compound fractions were similarly treated. Solutions in 95% ethanol were used

[14] Becker, *Ber.*, 1882, **15**, 2091.
[15] Basler, *Ber.*, 1883, **16**, 2716.
[16] Kuhn, *Org. Synth.*, 1933, **13**, 74.
[17] Schopff, *Ber.*, 1890, **23**, 1840; Ullman and Nadai, *Ber.*, 1908, **41**, 1872.
[18] Cf. Kehrmaren and Baumgartner, *Helv. Chim. Acta*, 1926, **9**, 673.
[19] Brewster and Groening, *Org. Synth.*, 1934, **14**, 66.
[20] Barclay and Campbell, *J.*, 1945, 530.
[21] Hayashi and Nakayama, *J. Soc. Chem. Ind. Japan*, 1933, **36**, 127.
[22] Weissburger and Weissburger, *J. Org. Chem.*, 1954, **19**, 968.
[23] Lindemann, *Ber.*, 1924, **57**, 555.

TABLE 4. *Products from nitration in acetic anhydride at 0° and 25°.*

Material	Wt. (g.)	Temp.	HNO_3 (g.)	Time (hr.)	Products and wts. (g.)	
Diphenylmethane ...	1·684	0°	0·63	65	CH_2Ph_2	1·346
					2-NO_2-deriv.	0·047
					4-NO_2-deriv.	0·043
					$COPh_2$	0·012
,, ...	1·687	25	0·63	16	CH_2Ph_2	1·390
					2-NO_2-deriv.	0·032
					4-NO_2-deriv.	0·052
					$COPh_2$	0·006
Fluorene	1·664	0	0·315	72	Fluorene	1·304
					2-NO_2-deriv.	0·165
					3-NO_2-deriv.	0·008
					4-NO_2-deriv.	0·089
,, ...	1·660	25	0·315	16	Fluorene	1·320
					2-NO_2-deriv.	0·198
					3-NO_2-deriv.	0·007
					4-NO_2-deriv.	0·084
Diphenyl ether	1·707	0	0·63	65	Ph_2O	1·134
					2-NO_2-deriv.	0·245
					4-NO_2-deriv.	0·235
,, ...	1·702	25	0·63	16	Ph_2O	1·243
					2-NO_2-deriv.	0·250
					4-NO_2-deriv.	0·249
Diphenylamine	0·339	0	0·063	20	$NHPh_2$	0·171
					N-Ac deriv.	0·049
					2-NO_2-deriv.	0·028
					N-Ac-2-NO_2-deriv.	0·054
					4-NO_2-deriv.	0·015
					N-Ac-4-NO_2-deriv.	0·010
,, ...	0·339	25	0·063	5	$NHPh_2$	0·184
					N-Ac deriv.	0·048
					2-NO_2-deriv.	0·027
					N-Ac-2-NO_2-deriv.	0·032
					4-NO_2-deriv.	0·015
					N-Ac-4-NO_2-deriv.	0·008
Carbazole	0·827	0	0·158	24	Carbazole	0·692
					N-Ac deriv.	0·001
					1-NO_2-deriv.	0·059
					2-NO_2-deriv.	0·002
					3-NO_2-deriv.	0·146
,, ...	0·836	25	0·158	6	Carbazole	0·752
					N-Ac deriv.	0·001
					1-NO_2-deriv.	0·032
					2-NO_2-deriv.	0·002
					3-NO_2-deriv.	0·079

TABLE 5. *Competitive nitrations.*

Material	Wt. (g.)	Temp.	HNO_3 (g.)	Time (hr.)	Products and wts. (g.)	
{ Diphenylmethane	1·681	0°	0·63	60	CH_2Ph_2	1·433
{ Diphenyl	1·540				NO_2-derivs.	0·066
					Ph_2	1·303
					NO_2-derivs.	0·060
{ Diphenylmethane	1·681	25	0·63	24	CH_2Ph_2	1·483
{ Diphenyl	1·542				NO_2-derivs.	0·061
					Ph_2	1·361
					NO_2-derivs.	0·090
{ Dibenzofuran	1·684	0	0·63	65	Dibenzofuran	1·499
{ Diphenyl	4·617				NO_2-derivs.	0·206
					Ph_2	4·387
					NO_2-derivs.	0·240
{ Dibenzofuran	1·682	25	0·63	17	Dibenzofuran	1·240
{ Diphenyl	4·621				NO_2-derivs.	0·284
					Ph_2	3·443
					NO_2-derivs.	0·252
{ Diphenyl ether	1·705	0	0·63	65	Ph_2O	1·396
{ Dibenzofuran	1·680				NO_2-derivs.	0·355
					Dibenzofuran	1·357
					NO_2-derivs.	0·187

XUM

in 0·5 cm. silica cells on a Unicam S.P. 500 spectrophotometer. The results are summarised in Table 4.

Competitive Nitrations.—The competitive nitrations were carried out in the same way as the simple nitrations, except that in the comparison carbazole–perylene a larger volume of acetic

TABLE 5. (*Continued.*)

Material	Wt. (g.)	Temp.	HNO_3 (g.)	Time (hr.)	Products and wts. (g.)	
{ Diphenyl ether	1·702	25°	0·63	17	Ph_2O	1·381
{ Dibenzofuran	1·681				NO_2-derivs.	0·458
					Dibenzofuran	1·349
					NO_2-derivs.	0·222
{ Fluorene	1·661	0	0·315	72	Fluorene	1·431
{ Diphenyl ether	1·700				NO_2-derivs.	0·241
					Ph_2O	1·453
					NO_2-derivs.	0·044
{ Fluorene	1·664	25	0·315	16	Fluorene	1·407
{ Diphenyl ether	1·664				NO_2-derivs.	0·294
					Ph_2O	1·425
					NO_2-derivs.	0·044
{ Perylene	0·504	0	0·063	21	Perylene	0·492
{ Carbazole	0·335				NO_2-derivs.	0·007
					Carbazole	0·295
					NO_2-derivs.	0·004
{ Perylene	0·504	25	0·063	5	Perylene	0·497
{ Carbazole	0·670				NO_2-derivs.	0·005
					Carbazole	0·655
					NO_2-derivs.	0·004
{ Diphenylamine	0·338	0	0·063	17	$NHPh_2$	0·231
{ Carbazole	3·346				NO_2-derivs.	0·048
					Carbazole	3·303
					NO_2-derivs.	0·028
{ Diphenylamine	0·338	25	0·063	5	$NHPh_2$	0·190
{ Carbazole	3·344				NO_2-derivs.	0·062
					Carbazole	3·332
					NO_2-derivs.	0·010

anhydride (1 l.) had to be used. The mixture of mononitro-compounds was analysed [4] as a binary mixture on the assumption that the isomer ratios were the same as in the simple nitrations. The results are shown in Table 5.

We thank Professor Weissberger for information concerning the nitration of fluorene, the University of London for a grant for spectroscopic equipment, Imperial Chemical Industries Limited for a gift of dinaphthalimide, and the Department of Scientific and Industrial Research for a maintenance grant (to D. S. U.).

QUEEN MARY COLLEGE, MILE END ROAD, LONDON, E.1.
[Present address (D. S. U.): STERLING CHEMICAL LABORATORY, YALE UNIVERSITY, NEW HAVEN, CONN., U.S.A.] [*Received, February 24th,* 1958.]

627. *The Chemistry of the Bile Pigments. The Structures of Stercobilin and d-Urobilin.*

By C. H. Gray and D. C. Nicholson.

Stercobilin and d-urobilin have been degraded with the formation of fragments from the end ring and middle ring of each. The structure of stercobilin as a hydrogenated i-urobilin, *i.e.*, mesobilene-b, has been confirmed and the β-positions of the end rings have been established as the sites of attachment of the extra hydrogen atoms. The production of ethylmethylmaleimide and hæmatinimide by the oxidation of d-urobilin and the quantitative hydrogenation of this pigment suggest that it is related to i-urobilin in that one ethyl group is replaced by a vinyl group. The isolation of two new urobilinoid pigments, namely, d-urobilin-IXα and racemic dehydro-i-urobilin, is described.

Most bile pigments are tetrapyrrolic compounds derived from biliverdin [4 : 5-di-2′-carboxyethyl-1 : 3 : 6 : 7-tetramethyl-2 : 8-divinylbilatriene-a,b,c (I)] by different degrees of reduction. They are classified according to the number and position of the double bonds joining the bridge carbon atoms (a,b,c, in I) to the pyrrole nuclei.[1] Biliverdin is formally derived from protoporphyrin-IX (II) by oxidative removal of the α-carbon linkage, and all naturally occurring bile pigments are therefore assumed to be IXα-compounds in that the arrangement of the β-substituents corresponds to that in biliverdin. Biliverdin and a number of related compounds have been synthesised and their IXα-structures established beyond doubt. Analytical evidence of this has also been obtained.[2] Pigments in which the vinyl groups have been reduced to ethyl groups are given the prefix " meso " because of their formal relation to mesoporphyrin (III). The structure usually assigned to biliverdin is the lactim form of the bislactam (I), but the lactam structure is more consistent with recent knowledge of the " hydroxypyrroles "[3] and of the bile pigments,[4] and is therefore used in this paper.

An important group of bile pigments includes the urobilins which are thought to be mesobilenes-b. These include stercobilin [5] ($[\alpha]_D$ −4000° in $CHCl_3$), d-urobilin [5,6] ($[\alpha]_D$ +5000° in $CHCl_3$), and the optically inactive i-urobilin. i-Urobilin receives the trivial name, urobilin-IXα, although all the naturally occurring bile pigments have the IXα-arrangement of β-side chains. Of these compounds only the structure of i-urobilin has been established by degradation and synthesis [7] as 4 : 5-di-2-carboxyethyl-2 : 8-diethyl-1 : 3 : 6 : 7-tetramethylbilene-b (XIV or XVI).

Elementary analyses suggest that stercobilin [8] and d-urobilin [6] are tetrahydro- and dehydro-derivatives, respectively, of i-urobilin. The two pigments cannot, therefore, be structural isomers or enantiomorphs as suggested by With [9] although the racemisation of d-urobilin described in this paper implies the existence of a true enantiomorph of that pigment. Both pigments presumably contain a dipyrromethene structure since their absorption spectra closely resemble those of i-urobilin [6] and the simple dipyrrylmethenes.[10] By the action of concentrated sulphuric acid stercobilin is converted into a glaucobilin (*i.e.*, a mesobiliverdin) which is identical with synthetic glaucobilin IXα; [8] stercobilin

[1] Lemberg and Legge, " Haematin Compounds and the Bile Pigments," Interscience Publ., Inc. New York, 1948, p. 107.
[2] Gray, Nicholson, and Nicolaus, *Nature*, 1958, **181**, 183.
[3] Decker and Plieninger, *Annalen*, 1956, **598**, 198.
[4] Birch, Smith, and Smith, personal communication.
[5] Lowry, Ziegler, and Watson, 1952, " Recent Studies of the Urobilin Problem," *Bull. Univ. Minnesota Hosp. & Med. Foundn.*, No. 7, 1952.
[6] Lowry, Cardinal, Collins, and Watson, *J. Biol. Chem.*, 1956, **218**, 633, 641.
[7] Siedel and Meier, *Z. physiol. Chem.*, 1936, **242**, 101.
[8] Fischer and Halbach, *ibid.*, 1935, **238**, 59.
[9] With, " Biology of the Bile Pigments," Arne Frost-Hansen, Copenhagen, 1954, p. 17.
[10] Pruckner and Stern, *Z. phys. Chem.*, 1938, *A*, **182**, 117.

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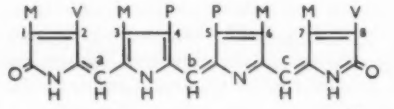
must therefore be a IXα-isomer and the same must be true of d-urobilin which undergoes smooth reduction to mesobilirubinogen (XIII) or (XV), the mesobilane corresponding to i-urobilin. The absence of ethylmethylmaleimide as an oxidation product of stercobilin has been noticed [8] and this has been interpreted as indicating that the extra hydrogen atoms in this pigment are located in the end rings. However, no further direct evidence has been put forward concerning the structures of stercobilin or d-urobilin.

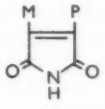
Stercobilin

Oxidative Products of Stercobilin.—The stercobilin used in our experiments was prepared by Watson's method,[11] by extraction from the fæces of normal subjects or patients with hæmolytic disease, and purified by repeated recrystallisation of the hydrochloride.

Preliminary experiments showed that stercobilin hydrochloride is fairly slowly oxidised by 0·74N-chromium trioxide solution in sulphuric acid, the pigment utilising about 38 equivalents per molecule and about 5 atoms of carbon per molecule being oxidised to carbon dioxide. Chromatographic examination of the products revealed the presence of acetic

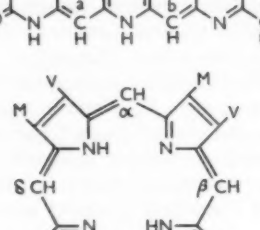


(I)

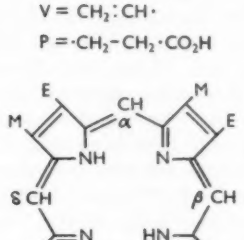


(IV)

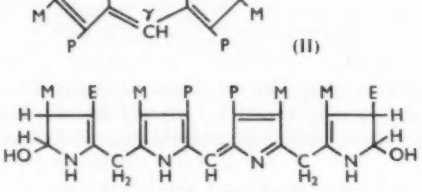
M = Me E = Et
V = CH_2:CH·
P = ·CH_2–CH_2·CO_2H



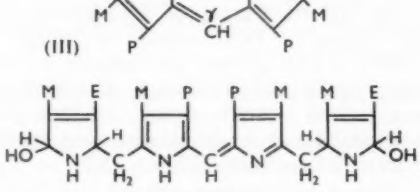
(II)



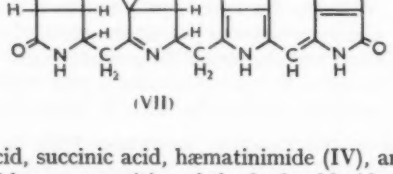
(III)



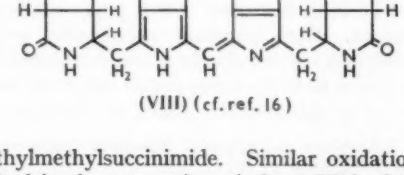
(V) (cf. ref. 8)



(VI) (cf. ref. 13)



(VII)



(VIII) (cf. ref. 16)

acid, succinic acid, hæmatinimide (IV), and ethylmethylsuccinimide. Similar oxidations of larger quantities of the hydrochloride resulted in the conversion of about 37% of the nitrogen to ammonia or a volatile amine and afforded sufficient succinic acid and ethylmethylsuccinimide for comparison with authentic compounds. The neutral fraction, invariably obtained as a weakly dextrorotatory oil, had ultraviolet and infrared spectra similar to those of authentic DL-ethylmethylsuccinimide, identity being confirmed by elementary analysis and hydrolysis to the acid. The natural imide was never obtained

[11] Watson, *J. Biol. Chem.*, 1934, **105**, 469.

crystalline and appeared to contain traces of unidentified substances which caused slight differences in its ultraviolet spectrum compared with those of authentic imide and the product of dry distillation of ammonium *meso*-ethylmethylsuccinate. Authentic DL-ethylmethylsuccinimide, prepared and isolated by a method similar to that used by Linstead and Whalley[12] for DL-$\alpha\alpha'$-dimethylsuccinimide, proved to be a readily crystallisable compound of low melting point and it is possible that the natural product was a mixture of the *meso*- and DL-isomers. The stereochemistry of these isomers and hence of stercobilin will form the subject of a subsequent paper.

Ethylmethylmaleimide and dihydrohæmatinimide appear to be absent from the oxidation products of stercobilin. Hæmatinimide, although shown chromatographically to be a product of oxidation from stercobilin, was never obtained crystalline. However, stercobilinogen, the dihydro-derivative of stercobilin obtained in a non-crystalline form by amalgam or catalytic reduction, afforded hæmatinimide in about 50% of the yield expected if stercobilin is assumed to contain two 3-carboxyethyl-4-methylpyrrole rings per molecule.

The Structure of Stercobilin.—Oxidative degradation of stercobilin to ethylmethylsuccinimide shows that the end rings are the sites of attachment of the extra hydrogen atoms, as in the structures (V) and (VI) which have been previously suggested,[8,13] although without direct evidence. Structures such as (VII), containing adjacent dihydropyrrole rings, also require consideration since they have a molecular asymmetry which is consistent with the optical activity of stercobilin and because they too would give rise to hæmatinimide, succinic acid, and ethylmethylsuccinimide on oxidation.

Succinic acid obtained by oxidation of pyrophæophorbide-a is interpreted as derived from the β-carboxyethyldihydro-β′-methylpyrrole ring.[14] Succinic acid formation from stercobilin and d-urobilin (see below) cannot have the same significance because d-urobilin, which is a dehydro-i-urobilin, cannot contain hydropyrrole rings. This acid therefore probably arises from stercobilin and d-urobilin by partial destruction of the 3-carboxyethyl-4-methylpyrrole rings in these pigments. Structures such as (VII) are excluded by the absence of ethylmethylmaleimide and dihydrohæmatinimide in the oxidation products and by the production of a fairly high yield of hæmatinimide on the oxidation of stercobilinogen. In the oxidation of mesoporphyrin, hæmatinimide is difficult to isolate in high yield and the isolation of an amount approximately equivalent to one 3-carboxyethyl-4-methylpyrrole ring is considered to indicate the presence of two such rings per molecule of pigment. In the simple dipyrrylmethenes the introduction of a hydroxyl group into an α-position of the dipyrrylmethene group caused a hypsochromic shift of about 60—70 mμ in the main spectral band.[15] The much smaller difference between the positions of the main spectral bands of stercobilin and i-urobilin is inconsistent with the structure (VII) for stercobilin. The low yield of ethylmethylsuccinimide (maximum, 30%) obtained in our experiments, the extensive ring destruction obvious from the quantitative oxidations, and the quantity of pigment nitrogen converted into ammonia or amine may indicate contributions from structures such as (V) and (VI) in which the presence of isolated double bonds would reduce ring stability towards oxidation. In this case the end rings of stercobilin would probably constitute a complex tautomeric system composed of the four well-known individual systems (" 3-carbon," C=C–C–H; " keto-enol," C=C–O–H; " imino-enamine," C=C–N–H; and " amido-imidol," O=C–N–H[16]) the elements of which are discernible in the structures shown. It is possible, therefore, that the end rings of stercobilin, in common with prototropic systems in general, will vary according to their environment. However, in the absence of such tautomerism, ethylmethylsuccinimide could arise only from structure (VIII) which bears the extra hydrogen atoms in the

[12] Linstead and Whalley, *J.*, 1954, 3722.
[13] Siedel and Grams, *Z. physiol. Chem.*, 1940, **267**, 49.
[14] Linstead, Ficken, and Johns, *J.*, 1956, 2272.
[15] Pruckner and Dobeneck, *Z. phys. Chem.*, 1942, *A*, **190**, 43.
[16] Baker, " Tautomerism," Routledge, London, 1934.

XUM

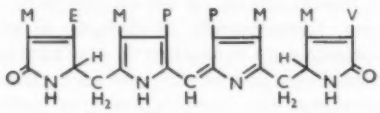
β-positions of the end rings; such a structure was first postulated by Birch,[17] and from the above considerations must be considered the most appropriate for stercobilin.

d-Urobilin

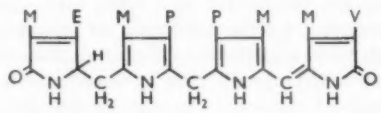
Oxidative Products of d-Urobilin.—d-Urobilin is usually obtained from infected fistula bile [18] or from the fæces of patients receiving antibiotic therapy,[5] but for the present investigation the material was isolated from the fæces of a patient with thalassemia and whose blood therefore contained a high proportion of fœtal hæmoglobin.

After oxidation of d-urobilin by 0·74N-chromium trioxide in sulphuric acid, hæmatinimide, succinic acid, and ethylmethylmaleimide were identified by paper chromatography. The last two substances were obtained crystalline and found to be identical with authentic compounds.

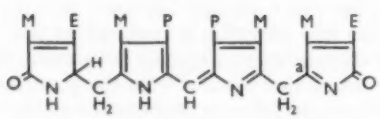
Catalytic Hydrogenation of d-Urobilin.—In methanol or acetic acid d-urobilin hydrochloride absorbed a maximum quantity of four equivalents of hydrogen per molecule in the presence of colloidal platinum. The *leuco*-compound thus obtained (tetrahydro-d-urobilin) was readily oxidised, by atmospheric oxygen or iodine, to give violet-brown solutions the dark colour of which made spectroscopic and polarimetric examination difficult; it was therefore impossible to assess accurately the amount of urobilin recovered and the optical activity retained. By avoiding prolonged solution of the pigment in chloroform it was possible to isolate as much as 12% of the original amount of d-urobilin as a crystalline dextrorotatory pigment. Quantitative hydrogenation showed that this pigment differed from the original d-urobilin, but resembled i-urobilin, in containing only one reducible double bond per molecule. Insufficient of this new compound was available for complete examination but the substance resembled d-urobilin in having an absorption maximum at 499 mμ in $CHCl_3$ and at 492 mμ in MeOH (extinction in the latter solvent being increased about three-fold on addition of free hydrogen chloride). If the hydrochloride is assumed to have an extinction coefficient equal to that of d-urobilin the pigment appears to have $[\alpha]_D$ +4950° in $CHCl_3$.



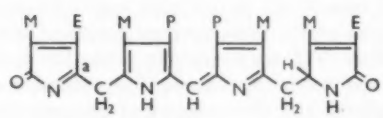
(IX)



(X)



(XI)



(XII)

Treatment of d-urobilin or the new pigment with dilute aqueous alkali led to loss of optical activity and partial isomerism to violet pigments. Quantitative hydrogenation of the crystalline, racemised d-urobilin revealed the presence of two reducible double bonds per molecule.

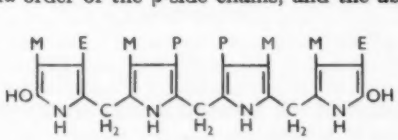
Pigments Obtained by Oxidation and Isomerisation of d-Urobilin.—Treatment of d-urobilin with excess of methanolic ferric chloride according to a method used by Legge for i-urobilin [19] caused only partial oxidation, up to 30% of the pigment being recovered as a urobilin. The products of this oxidation were separated into biliviolinoid and glaucobilinoid pigments by methods described in the Experimental section. The biliviolinoid pigments resemble those obtained similarly from i-urobilin.

[17] Birch, *Chem. and Ind.*, 1955, 652.
[18] Schwartz and Watson, *Proc. Soc. Exp. Biol. Med., N.Y.*, 1942, **49**, 641.
[19] Legge, *Biochem. J.*, 1949, **44**, 105.

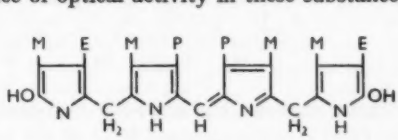
Violet pigments obtained by isomerisation in alkali of d-urobilin were separable into acid-, ether-, and chloroform-soluble fractions. The last-mentioned fraction contained most of the pigment as well as considerable unchanged urobilin. After removal of the urobilin the violet pigment showed an absorption maximum at 565 mμ in $CHCl_3$. The ethanolic zinc complex, with or without added iodine, was indistinguishable in its spectral properties from the same derivative of the products of oxidation.

The Structure of d-Urobilin.—The production of ethylmethylmaleimide by oxidation of d-urobilin indicates the presence of one or more 3-ethyl-4-methylpyrrole rings per molecule, provided that prototropic changes have not occurred. The absorption of four equivalents of hydrogen in the conversion of the pigment into a *leuco*-compound, presumably a dextrorotatory isomer of i-urobilin (see below), indicates that it is a dehydro-i-urobilin and this confirms Watson's conclusion [6] from elementary analyses. Because the dipyrrylmethene chromophore is unmodified the extra unsaturation in d-urobilin must be located either in the substituents in the 1-, 2-, 7-, or 8-position or in some nuclear position, for example, position (a) in (XI) and (XII), in which conjugation is impossible. The only obvious formulæ conforming to this requirement and to the available evidence are (IX) (or the isomer having interchanged ethyl and vinyl groups), (X), (XI), and (XII). Structures (XI) and (XII), because of the presence of one asymmetric carbon atom, could exhibit the optical activity shown by d-urobilin but could presumably arise only if biliverdin—which bears a hydrogen atom on each nitrogen atom—were an easily tautomerising substance. Structures such as (X) (α-hydroxydipyrrylmethenes in a pyrrolinone form) are improbable for the same reason that on spectroscopic grounds structure (VII) is inappropriate for stercobilin. Structures such as (IX) therefore appear to be the most probable for d-urobilin. The presence of a vinyl group, although not demonstrated experimentally, is considered more likely than that of an ethylidene group which has never been found in the bile pigments.

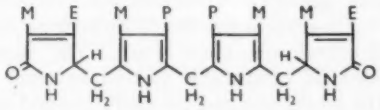
The isolation of a dextrorotatory pigment after mild oxidation of tetrahydro-d-urobilin was unexpected. If structure (IX) is correct for d-urobilin, tetrahydro-d-urobilin should be identical with mesobilirubinogen. This is a substance of known structure which forms i-urobilin on mild oxidation, and is formed on reduction of d-urobilin under conditions which favour racemisation [5] (*e.g.*, sodium amalgam or alkaline ferrous hydroxide). The usually accepted structures for mesobilirubinogen (XIII) and i-urobilin (XIV) imply the absence of any element of asymmetry apart from that which is inherent in the asymmetric IXα order of the β-side chains, and the absence of optical activity in these substances is



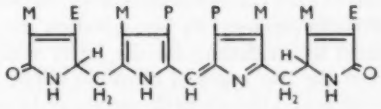
(XIII)



(XIV)



(XV)



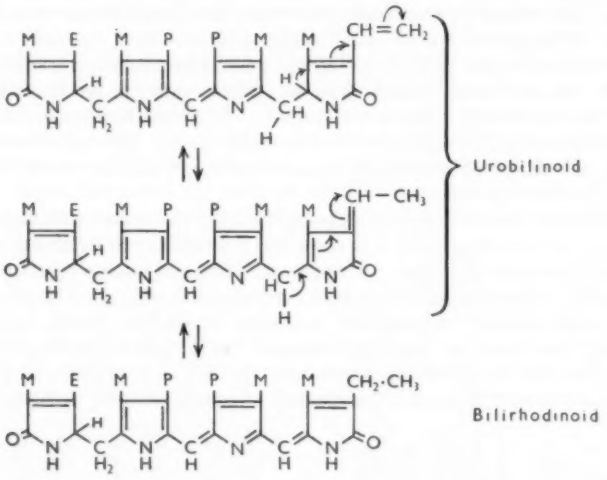
(XVI)

therefore consistent with such structures. However, the respective pyrrolinone and bislactam formulæ (XV and XVI) each contain two asymmetric carbon atoms per molecule and optical isomerism is then possible for mesobilirubinogen or for the urobilin of which it is the chromogen. We therefore suggest that the dextrorotatory urobilin obtained on oxidation of tetrahydro-d-urobilin is an optically active isomer of i-urobilin which would therefore be either an optically *meso*-compound or a racemic mixture of which the new

dextrorotatory urobilin is a component. The IXα-order of the β-side chains, confirmed analytically for d-urobilin and many of the other bile pigments,[2] must also obtain in the new pigment. We therefore suggest that this be called " d-urobilin-IXα " analogous to the name " urobilin-IXα " used for i-urobilin.

The conversion of d-Urobilin into Biliviolinoid Pigments.—Both i-urobilin and d-urobilin are readily dehydrogenated to biladienes and bilatrienes on treatment with ferric chloride. d-Urobilin appears to undergo this change under conditions in which oxidation is impossible. After treatment of an ethanolic solution of the hydrochloride with potassium *tert.*-butoxide, sodium hydroxide, or piperidine, addition of acetic acid produced a violet colour which was not obtained in control experiments in which addition of base was omitted. This colour reaction proceeded equally well when oxidation was excluded either by the passage of a stream of hydrogen or by the addition of sulphite. Even the strong reducing environment of tetrahydrofuran containing suspended lithium aluminium hydride failed to inhibit the production of violet pigment. Changes under these conditions cannot be oxidations and reduction could not lead to the formation of biliviolins. If the validity of structure (IX) for d-urobilin is assumed, simple tautomerisation to a mesobiliviolin or mesobilirhodin may be formulated as in Scheme *A*.

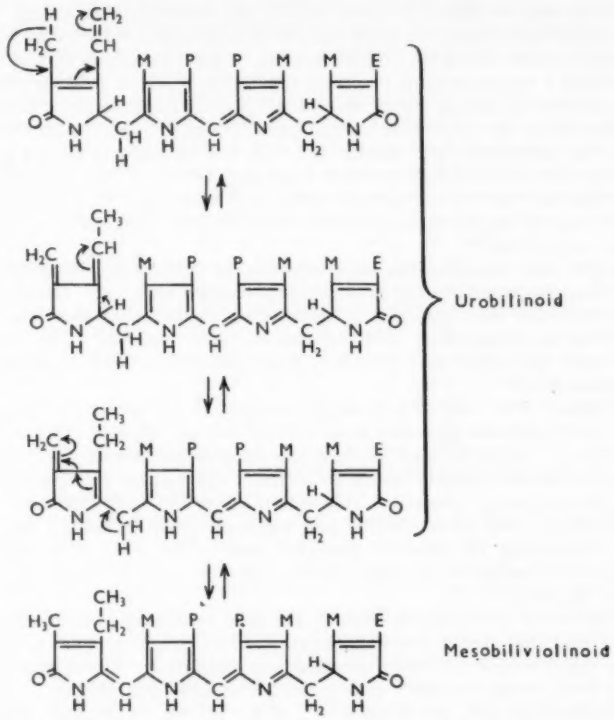
A



Similar changes, but involving hyperconjugation of the 1-methyl group, are possible if the vinyl group is assumed to be in the position 2 (Scheme *B*).

If compounds with structures (XI) and (XII) were found in Nature they would be capable of even simpler isomerisation to biliviolinoid pigments. If such modes of formation of biliviolin pigments by isomerisation are correct, these pigments should differ from those obtained by oxidation, for the latter would still contain one vinyl group. The relation between the two types of biliviolin might be somewhat comparable to that between the biliverdins and the mesobiliverdins, or between the biliverdins and the bilirubins and their dihydro-derivatives respectively. On treatment with iodine of the zinc complex of biliverdin the absorption band in the red is at 624 mμ. but that of mesobiliverdin is at 640 mμ.[20] However, the zinc complexes of mesobilirubin (with two ethyl groups) and of dihydrobilirubin (with one vinyl and one ethyl group), as well as of mesobiliverdin (with two ethyl groups) and dihydrobiliverdin (with one vinyl and one ethyl group), show no such spectroscopic difference after treatment with iodine. The same derivatives of the

[20] Plieninger, *Z. physiol. Chem.*, 1942, **274**, 231.



biliviolins obtained from d-urobilin have no such discrete bands in the red part of the spectrum, so that it was impossible to apply this method for distinction of the two types of biliviolin expeeted to arise.

Experimental

Microanalyses and quantitative micro-hydrogenations were carried out by Miss J. Cuckney and her colleagues at the Imperial College of Science. M. p.s were determined in the Kofler apparatus. Optical rotations were measured at 20—25°. Ultraviolet spectra were determined by using the Hilger spectrophotometer. Solvents were redistilled; and ether was freed from peroxide by treatment with ferrous sulphate solution. For column chromatography Savory and Moore's alumina, B.D.H. chromatographic calcium carbonate, and B.D.H. talc and magnesium oxide were used.

Paper Chromatography.—Descending development on Whatman No. 1 paper was used. The following solvents were used: (A) Xylene–phenol–85% formic acid (7 : 3 : 1, w/w/v) [21]; (B) ethanol–water–ammonia (*d* 0·88) (80 : 16 : 4 v/v/v); [22] (C) water-saturated ethyl acetate; (D) butan-1-ol–formic acid (95 : 5) saturated with water; [23] (E) pyridine–ammonia–water (6 : 2 : 1); [23] (F) butan-1-ol saturated with 1·5N-ammonia.[24]

Acidic compounds were located on the chromatograms by spraying the chromatograms with a solution of Bromocresol Green made just blue by addition of sodium hydroxide solution. Imides were detected by exposure to chlorine, aeration, and subsequent spraying with starch (0·25%) and potassium iodide (5%) solution. Chromatograms known to contain imides only were given the latter treatment without previous spraying with indicator. Authentic compounds were used as markers on the same paper.

[21] Kalbe, *ibid.*, 1954, **297**, 21.
[22] Long, Steadman, and Quale, *J.*, 1951, 2197.
[23] Linstead, Ficken, and Johns, *J.*, 1956, 2280.
[24] Brown and Hall, *Nature*, 1950, **67**, 166.

XUM

Reference Compounds.—Authentic *meso-* and DL-ethylmethylsuccinic acid were prepared and separated by methods similar to those used by Linstead and Whalley for the preparation of the αα′-dimethylsuccinic acids.[12] Dry distillation of the ammonium salt of the pure *meso*-acid always afforded a non-crystalline or poorly crystalline imide of poor elementary analysis, presumably a mixture of impure *meso-* and DL-ethylmethylsuccinimide. Similar treatment of the ammonium salt of the unpurified DL-acid gave a readily crystallisable imide (m. p. 56°) of good analysis for ethylmethylsuccinimide and this was assumed to be the pure DL-isomer.

Hæmatinimide and ethylmethylmaleimide were obtained by hydrolysis and oxidation of mesoporphyrin dimethyl ester by the method of Muir and Neuberger.[25] *meso-* and DL-Dihydrohæmatinic acids and DL-dihydrohæmatinimide were obtained according to the method of Linstead, Johns, and Ficken.[23]

Dihydrobilirubin and mesobilirubin were obtained by quantitative hydrogenation of bilirubin in 0·1N-sodium hydroxide in the presence of palladised charcoal. Glaucobilin, dihydrobiliverdin, and biliverdin were obtained in solution by oxidation of mesobilirubin, dihydrobilirubin, and bilirubin respectively with methanolic ferric chloride. The required verdins were extracted, first, into ether and then into 2·8N-hydrochloric acid from which they were extracted into chloroform.

Ethylmethylsuccinic Acid.—Ethyl α-bromopropionate (72 g.) was slowly added to a stirred solution of ethyl sodiomalonate prepared from sodium (9·2 g.), ethanol (150 ml.), and diethyl ethylmalonate (75 g.). After 6 hours' boiling, the ethanol was distilled off; the residue was dissolved in chloroform and washed free from halide. The residue was distilled, the fraction boiling at 165°/24 mm. being collected. This redistilled at 280—282°/760 mm. The product, a viscous syrup (35 g.), was again distilled and was hydrolysed in boiling 36% hydrochloric acid for 48 hr. On cooling, the solution deposited meso-*ethylmethylsuccinic acid* (7 g.) which was recrystallised to constant m. p. (187°) from water (Found: C, 52·6; H, 7·8. $C_7H_{12}O_4$ requires C, 52·4; H, 7·5%).

Ethylmethylsuccinimide from the meso-*Acid.*—The *meso*-acid (3·5 g.) was dissolved in ammonia (75 ml.; *d* 0·880), and the solution was evaporated almost to dryness. The residue was heated at 120° and the light yellow oil which distilled was discarded. Distillation was continued until, at 250°, a thick syrup distilled; this redistilled at 160—163°/25 mm.; it partially, but never wholly, crystallised (2·1 g.) (Found: C, 58·5; H, 8·0. $C_7H_{11}O_2N$ requires C, 59·5; H, 7·8%). The *product* in EtOH showed increasing light absorption from 270 to 220 mμ with an inflexion ($E^{1\%}_{1\,cm.}$ 3·8) at 248 mμ.

DL-*Ethylmethylsuccinimide.*—The mother-liquors remaining after the crystallisation of the *meso*-acid were exhaustively extracted with ethyl acetate. Evaporation of the dried extract gave a non-crystallisable syrup. Concentrated ammonia solution was added until the mixture was alkaline and the solution was diluted, with water, to 100 ml. A small quantity of unhydrolysed ester was extracted into chloroform, and the syrup obtained by evaporation of the whole solution was dry-distilled at 130—280°/760 mm. Crystallisation from water furnished a *product* of m. p. 54—55° (2·3 g.) (Found: C, 59·4; H, 8·0; N, 9·8. $C_7H_{11}O_2N$ requires C, 59·5; H, 7·8; N, 9·9%), showing increasing absorption in EtOH from 270 to 220 mμ with one inflexion ($E^{1\%}_{1\,cm.}$ 6·2) at 248 mμ.

meso*Dihydrohæmatinic Acid.*—Sodium (6·2 g.) was dissolved in ethanol (200 ml.). To the cooled, stirred solution ethyl cyanoacetate (30 g.) was added. About a third of the alcohol was removed, and ethyl α-bromopropionate (48 g.) was slowly added with stirring. When deposition of sodium bromide had ended the mixture was boiled, under reflux, until no longer alkaline. Volatile material was distilled off and water was added to the residue. The organic fraction was extracted into ether and washed free from halide. After drying (Na_2SO_4) and removal of ether the residue was distilled, the fraction of b. p. 159°/30 mm. (26 g.) being collected. The yield of redistilled diethyl α-cyano-α′-methylsuccinate, b. p. 156°/20 mm., was 20 g.

Sodium (2·2 g.), dissolved in ethanol (30 ml.), was quickly added to a stirred solution of the diethyl α-cyano-α′-methylsuccinate (20 g.) in ethanol (30 ml.). Ethyl β-bromopropionate (25 g.) was slowly added and the mixture was heated at 90° for 10 hr., then being neutral to litmus. Volatile solvent was removed and the ester separated in the way described above. A small amount of unchanged ethyl β-bromopropionate was removed and the residue was distilled, giving a fraction of b. p. 220°/38 mm. (19 g.). The product was hydrolysed by boiling with 36% hydrochloric acid (200 ml.) for 20 hr. A small quantity of unhydrolysed ester was

[25] Muir and Neuberger, *Biochem. J.*, 1949, **45**, 164.

separated from the hot mixture which was then concentrated to 50 ml. and cooled. The *meso*-acid which crystallised at this stage was recrystallised from acetone to constant m. p. (176—178°) (4 g.; a further quantity was recovered from mother-liquors—see below) (Found: C, 47·1; H, 5·9. Calc. for $C_8H_{12}O_6$: C, 47·0; H, 5·9%).

DL-*Dihydrohæmatinic Acid.*—The mother-liquor from the preparation of the *meso*-acid was continuously extracted with ether for several days; this solution, on cooling, deposited 2·5 g. of acid, m. p. 141°, which recrystallised from acetone to the correct m. p. for the *meso*-acid, bringing the total yield of that isomer to 6 g. Evaporation of the ethereal solution afforded a solid which was heated for 3 hr. at 200°. The product was boiled with dilute hydrochloric acid and charcoal, filtered, and evaporated to dryness. The residue was recrystallised from acetone to constant m. p. (144°) (0·9 g.) (Found: C, 47·1; H, 5·9%).

DL-*Dihydrohæmatinimide.*[23]—*meso*-Dihydrohæmatinic acid (2·2 g.) and urea (0·81 g.) were fused together at 185° until no more carbon dioxide was evolved (1 hr.). The cooled mass dissolved in water was acidified with 36% hydrochloric acid (5 ml.), and the imide was extracted continuously into ethyl acetate. The extract was washed with a small quantity of water and filtered. The syrup obtained by evaporation of the ethyl acetate was redissolved in fresh solvent and warmed with benzylamine (1 ml.). The precipitated benzylamine salt was recrystallised to constant m. p. (153°) from methyl alcohol–ethyl acetate (yield 0·5 g.). The benzylamine salt was dissolved in cold water (20 ml.) and the solution was acidified. The liberated imide was extracted into ether and washed with a little water. Evaporation of the solvent left a syrup which slowly crystallised *in vacuo* over sulphuric acid (m. p. 85—86°) (Found: N, 7·5. Calc. for $C_8H_{11}O_4N$: N, 7·6%).

Isolation of Stercobilin Hydrochloride. (*Watson's method* [11] *with minor modifications*).—Fæces were exhaustively extracted with ethereal acetic acid. The residue, left after distillation of the extract, was poured into 6 volumes of 1% w/v hydrochloric acid, and left for 16 hr. After filtration from fat and neutralisation with potassium acetate, porphyrins were removed by ether. Stercobilin was then removed from the aqueous solution by exhaustive extraction with chloroform and was re-extracted from the chloroform into water. The free urobilin in aqueous solution was converted into the hydrochloride by addition of 9% v/v hydrochloric acid and was again extracted into chloroform. The concentrated solution of stercobilin, obtained by almost complete evaporation of the chloroform solution, was poured dropwise into light petroleum, and the precipitated pigment was crystallised from cold, dry acetone. Further purification to high optical activity was achieved by recrystallisation from chloroform (containing a trace of methanol in the later stages) and then from methanol–ethyl acetate. This procedure provided a product of $[\alpha]_D$ −3000° or less (in $CHCl_3$) and this was increased by drying the substance over phosphoric oxide *in vacuo* at 60—70°. Yields ranged from 7 to 130 mg. of hydrochloride per 100 g. of moist fæces, $[\alpha]_D$ ranging from −3150° to −3850° in $CHCl_3$ (lit.,[5] −4000°). Fæces from normal subjects rarely afforded worthwhile quantities of pigment; considerably larger yields were obtained from the fæces of patients with hæmolytic disease.

Isolation of d-Urobilin.—The method outlined for stercobilin was followed with fæces from a subject with thalassæmia, but much less ether was used for the extraction of porphyrins and the solution, after the precipitation of fats, was worked up after only 30 min. In later preparations 10—20 ml. of 1% iodine solution were added at this stage to increase the rate of conversion of the extracted d-urobilinogen into d-urobilin. Storage overnight as in the stercobilin preparations gave much violet pigment with less urobilin and more difficulty in purification. When fairly pure, d-urobilin hydrochloride is less soluble in chloroform than is stercobilin hydrochloride and in the later stages of recrystallisation it was necessary to incorporate about 10% (v/v) of methanol in the chloroform. The added methanol was partly removed by evaporation of the filtered solution whilst fresh chloroform was continuously added. Crystallisation continued easily when the solution was cooled at the first sign of deposition of pigment. The product so obtained was finally freed from occluded chloroform by crystallisation from methanol–ethyl acetate and was dried in the same way as stercobilin but at 35—40°. Yields ranged from 10 to 50 mg. of hydrochloride per 100 g. of moist fæces and $[\alpha]_D$ from +4100° to +4700° (lit.,[6] +5000°).

Examination of chloroform solutions containing 1·35—0·13 mg. of urobilin hydrochloride per 100 ml. gave $E^{1\%}_{1\,cm.}$ 1450 at 499 mμ.

25·79 mg. of hydrochloride absorbed 1·82 ml. of hydrogen at N.T.P. (theor. for 2 double bonds 1·85 ml. at N.T.P.). 29·50 mg. absorbed 2·09 ml. of hydrogen at N.T.P. (theor. 2·12 ml.).

XUM

Quantitative Experiments on the Oxidation of Stercobilin Hydrochloride.—Crystalline stercobilin hydrochloride was suspended in 50% (v/v) aqueous sulphuric acid at 0° and an equal volume of 1·48N-chromium trioxide solution was slowly added. The reaction was allowed to proceed at room temperature for 64—67 hr. Evolved carbon dioxide was aspirated, in a stream of nitrogen, into tubes containing 2N-sodium hydroxide or N-barium hydroxide. In the former case barium carbonate was precipitated by the addition of 20% barium chloride solution, washed, dried, and weighed; in the latter, residual barium hydroxide was titrated, in the presence of acetone, with standard acid.[35] The reaction mixture was diluted and residual oxidant was estimated iodometrically. The results were calculated as atoms of carbon, per molecule of pigment, converted into carbon dioxide and equivalents of oxidation consumed. These results are in the Table.

Stercobilin hydrochloride used (mg.)	$[\alpha]_D$ ($CHCl_3$)	Equivs. of oxidant added per mol.	C atoms/mol. oxid. to CO_2	Equivs. oxidant consumed
26·5	−3340°	49·3	—	38·6
23·0	−3773	56·8	4·8	38·2
20·0	−3773	75·0	5·6	39·5
22·0	−3773	67·8	5·3	38·2
22·0	−3773	42·5	4·8	37·5
100·0	−3335	36·6	4·4	33·0

Oxidation of Stercobilin Hydrochloride with Isolation of Succinic Acid and Ethylmethylsuccinimide.—Stercobilin hydrochloride (225 mg., $[\alpha]_D$ −3850° in $CHCl_3$), suspended in 50% (v/v) aqueous sulphuric acid (8·75 ml.), was stirred at −5° during the slow addition of 1·48N-aqueous chromium trioxide (8·75 ml., 36 equivs. per mol.). Stirring was continued for 6 hr. during which the solution was allowed to attain room temperature. After 48 hr. residual oxidant was destroyed by sodium hydrogen sulphite, and volatile material was aspirated into 2 : 4-dinitrophenylhydrazine solution by a stream of nitrogen; no precipitate of phenylhydrazone was produced. The reaction mixture was diluted with water (10 ml.), and the products of oxidation were removed in two main fractions by extraction, first with chloroform (3 × 30 ml.), then with ethyl acetate (5 × 30 ml.). Paper chromatography of the chloroform extract at this stage, with solvent F, revealed an acidic substance R_F 0·12 corresponding to formic acid and acetic acid which are not separable in this system. The compound was assumed to be acetic acid because of its failure to reduce ammoniacal silver nitrate solution. Each extract was washed twice with water (2 ml.), dried by filtration, and evaporated. The original aqueous solution then contained 7·4 mg. of nitrogen (*i.e.*, 37% of the nitrogen originally present in the stercobilin). Continuous ether-extraction removed a minute quantity of syrup which contained succinic acid (R_F 0·12—0·13 in solvent A), leaving in the aqueous phase 4·97 mg. of nitrogen of which 4·34 mg. were present as ammonia or a volatile amine, displaceable by boiling alkali. Evaporation of the ethyl acetate extract afforded a semicrystalline mass (108·6 mg.) which dissolved completely in acetone (2 ml.). 0·01 ml. quantities of the solution were used for paper chromatography with the following results. In solvent E: R_F, 0·11 (acid) not identified, 0·22 (acid) (cf. succinic acid R_F 0·20), 0·45 (acid imide) faint and unidentified, 0·60 (acid imide) (cf. hæmatinimide R_F 0·62), and 0·79 (imide) (cf. DL-ethylmethylsuccinimide R_F 0·77). In solvent A: R_F 0·10 (acid) (cf. succinic acid R_F 0·10), 0·36 (acid imide) (cf. hæmatinimide R_F 0·36), 0·54 (acid imide) faint and unidentified, and 0·80 (imide) (cf. DL-ethylmethylsuccinimide R_F 0·78). After removal of the acetone the products from the ethyl acetate extract were dissolved in water (10 ml.), a small quantity of insoluble succinic acid (m. p. and mixed m. p.) was removed, and the solution was made alkaline by N-sodium hydroxide (2 ml.). Ether-extraction at this stage removed no material. The solution was brought, successively, to pH 6, 4, and 2 by addition of hydrochloric acid, with extraction at each stage with ether (100 ml.). Extraction at pH 6 removed a yellow oil (13·5 mg.) which did not crystallise but contained hæmatinimide (R_F 0·85 in solvent C, 0·48 in solvent B, and 0·56 in solvent E). The semicrystalline materials obtained by evaporation of the extracts of pH 2 and 4 (29·2 and 50·8 mg. respectively) were shown to be identical by paper chromatography. They were united and resolved, on silica gel in ether, into two main fractions: succinic acid (total 12·6 mg.) (m. p. and mixed m. p.) and a minor imide fraction (R_F 0·48 in solvent B and 0·85 in solvent C, corresponding to hæmatinimide).

Evaporation of the chloroform extract left a clear oil (66·4 mg.). This in fresh chloroform (0·5 ml.) exhibited a slight positive rotation in sodium light (0·2° in a 0·5 dm. tube). Paper

chromatography of the solution gave the following results. Solvent E: R_F 0·20 (acid) probably succinic acid, 0·57 (acid imide) (cf. hæmatinimide R_F 0·62), 0·71 (imide) (cf. DL-ethylmethylsuccinimide R_F 0·77). Solvent D: R_F 0·75 (imide) (cf. DL-ethylmethylsuccinimide R_F 0·75). Solvent A: R_F 0·30 (acid imide) (cf. hæmatinimide R_F 0·30), 0·60 (acid imide) faint and unidentified, 0·78 (imide) (cf. DL-ethylmethylsuccinimide R_F 0·78). The oil was dissolved in benzene (2 ml.) and eluted with the same solvent from a column of silica gel (water-saturated and allowed to dry in air). All fractions containing imide were united and on evaporation gave 25·8 mg. of crude imide. This was distilled in a micro-sublimation apparatus at 13—17 mm. The middle fraction (17 mg.) was twice redistilled, to give a straw-coloured oil (13·9 mg.) which did not crystallise even when seeded with DL-ethylmethylsuccinimide (Found: C, 59·5; H, 7·9. Calc. for $C_7H_{11}O_2N$: C, 59·5; H, 7·8%).

Identification of the Natural Imide.—The neutral, chloroform-soluble syrup obtained in the above experiment and authentic DL-ethylmethylsuccinimide in methanol (10^{-4} g. in 0·02 ml.) were used for chromatography in solvent B. The natural product gave spots of R_F 0·78 and 0·73 (two chromatograms) corresponding to R_F 0·78 and 0·79 for the authentic DL-imide. A mixture of authentic and the natural imide gave a single spot.

Both the oxidation product and authentic imide in ethanol had absorption maxima below 220 mμ, with an inflexion at 248 mμ ($E^{1\%}_{1\,cm.}$ 7·5 and 6·2 respectively). The curve for the oxidation product had also a slight inflexion at 280 mμ ($E^{1\%}_{1\,cm.}$ 1·8). Chloroform solutions of the natural and the authentic imide and the product of dry distillation of ammonium *meso*-ethylmethylsuccinate had infrared maxima at 1780 s, 1725 vs, 1458 m, 1382 m, 1347 s, 1286 m, and 1172 s, cm.$^{-1}$.

The above three compounds (4 mg. each) were heated (80°; 2 hr.) with concentrated hydrochloric acid (0·5 ml. for each) in sealed tubes, then diluted with water (0·5 ml.) and extracted with ether (10 ml.). The ethereal solutions were filtered and evaporated, and each residue was dissolved in ethanol (0·2 ml.); used for paper chromatography with solvent A, each gave one acid spot (R_F 0·47) corresponding to R_F 0·47 for DL- and *meso*-ethylmethylsuccinic acid.

Attempt to detect Dihydrohæmatinimide after Oxidation of Stercobilin Hydrochloride.—The ethyl acetate extract of the oxidation products of stercobilin hydrochloride (27 mg.) with 1·48N-chromium trioxide solution (1·05 ml.) and 50% v/v aqueous sulphuric acid (1·05 ml.) was used in methanol (1 ml.) for paper-chromatographic comparison with hæmatinimide (0·052 mg. in 0·02 ml. of methanol; R_F 0·85) and DL-dihydrohæmatinimide (same concn., R_F 0·71) with solvent C. Spots at the correct position for hæmatinimide and succinic acid were obtained and the mixture of products of oxidation and DL-dihydrohæmatinimide gave double spots (R_F 0·78, 0·70). In the same system DL-dihydrohæmatinic acid had R_F 0·54.

Oxidation of Stercobilinogen.—Stercobilin hydrochloride (50 mg.; $[\alpha]_D$ −3700° in $CHCl_3$) in 0·5N-sodium hydroxide (10 ml.) was reduced with hydrogen in the presence of colloidal palladium. After acidification with sulphuric acid the solution was extracted with light petroleum (250 ml.). The extract was washed with water (2 × 10 ml.), filtered, and evaporated. N-Chromium trioxide (3·2 ml., *ca.* 40 equiv.) and 20% hydrochloric acid (5 ml.) were added to the residue. The solution was kept at 20° for 15 hr., diluted with water (20 ml.), and extracted with chloroform. Spectroscopic examination of the diluted chloroform extract showed the presence of *ca.* 6·4 mg. of unchanged urobilin. The residue given by evaporation of the chloroform extract was dissolved in ethyl acetate. The original aqueous solution was extracted with the same solvent (100 ml.), and the two solutions were united. The residue remaining after the evaporation of the ethyl acetate was dissolved in water (10 ml.) and adjusted to pH 7 by sodium hydrogen carbonate. Extraction with chloroform at this stage removed a small amount of yellow material but evaporation of the extract left a negligible residue. The aqueous solution was brought to pH 5 by hydrochloric acid, and acetate buffer (pH 5·2) was added. Extraction with ethyl acetate then removed a syrup which was chromatographed in methanol (0·5 ml.) on Whatman No. 1 paper with water-saturated ethyl acetate; the appropriate section of the paper (R_F 0·8) was eluted with methanol, and the solution was evaporated to a syrup which crystallised after storage over sulphuric acid and seeding with authentic hæmatinimide (m. p. and mixed m. p. 118°; 12 mg.).

Oxidation of d-Urobilin Hydrochloride.—To d-urobilin hydrochloride (67 mg.; $[\alpha]_D$ +4520° in $CHCl_3$), suspended in 50% v/v aqueous sulphuric acid (2·6 ml.) at 0°, was added 1·48N-chromium trioxide solution (2·6 ml.). The mixture was kept at 20° for 44 hr., then treated with a trace of sodium hydrogen sulphite and extracted with chloroform (4 × 10 ml.). The

extract was washed with water (2 ml.), which was added to the original aqueous solution. The latter was then extracted with ethyl acetate (4 × 10 ml.), and the extract was washed as before. The chloroform and ethyl acetate solutions were dried by filtration and evaporated at 20°. The residual syrup from the chloroform extract crystallised when seeded with ethylmethylmaleimide (m. p. 58—60°) (11 mg., 36·7% of the yield possible if two 3-ethyl-4-methylpyrrole rings are present per molecule). The crystalline product was cautiously sublimed and crystallised from water, to give 8·6 mg. of m. p. 65° (mixed m. p. 66°). The infrared characteristics of the oxidation product and of authentic imide in potassium chloride were identical: 1765 s, 1710 s, 1455 m, 1385 m, 1350 s, 1175 m, 1065 m, 1055 m, 945 w, 735 m, cm.$^{-1}$. In spite of this identity the oxidation product appeared to contain small amounts of hæmatinimide and succinic acid (see paper chromatography below).

The residue obtained from the ethyl acetate extract was dried at 40° *in vacuo*, giving white semicrystalline material. A little chloroform at 0° removed a slightly dextrorotatory syrup (16·6 mg.) and the residual solid was sublimed at 13 mm. (m. p. 180—182° alone or mixed with succinic acid) (8·6 mg., 34% of the yield for complete destruction of two 3-carboxyl-4-methylpyrrole per molecule of pigment). Continuous ether-extraction of the original aqueous solution removed no further product, and the aqueous solution then contained 2·34 mg. of nitrogen (39% of the original pigment-nitrogen) of which 2·1 mg. (35% of the original nitrogen) were displaceable as ammonia or amine by boiling alkali.

The ethylmethylmaleimide (A) (8·6 mg.), the residue (B) (16·6 mg.) obtained by evaporation of the chloroform-washings of the ethyl acetate-soluble substance, and the chloroform-insoluble product (C) (8·6 mg.) were dissolved in methanol (1·72, 3·2, and 1·72 ml. respectively); 0·02 ml. of each solution was used for paper-chromatography in solvent C with the following results. A, spots at R_F 0·90 (cf. ethylmethylmaleimide 0·90) 0·40 (cf. succinic acid 0·40) (faint), and 0·78 (cf. hæmatinimide 0·78) (faint). B, spots at R_F 0·38 (cf. succinic acid 0·40), 0·78 (cf. hæmatinimide 0·76), and 0·15 unidentified. C, R_F 0·43 (cf. succinic acid 0·43).

Catalytic Reduction of d-Urobilin Hydrochloride and Isolation of d-Urobilin-IXα.—d-Urobilin hydrochloride (105·3 mg., $[\alpha]_D$ +4390° in $CHCl_3$) in acetic acid (10 ml.) in the presence of Adams platinum (33 mg.) absorbed 7·9 ml. (N.T.P.; 2 mols.) of hydrogen. The solution was then diluted with water (75 ml.), treated with 0·1N-iodine (2 ml.), and shaken with successive small quantities of chloroform until no further colour was removed; a further 1 ml. of iodine solution was added to the aqueous phase, and the chloroform extraction was repeated. Addition of iodine and extraction was continued until conversion of the *leuco*-compound into urobilin and extraction of the latter were complete. The aqueous solution finally gave no reaction with Ehrlich's reagent. Each successive portion of chloroform extract obtained was at once extracted with water (*i.e.*, the urobilin was removed as soon as possible from the chloroform in which it appeared to undergo rapid change to deeply coloured compounds). To the aqueous solution of free pigment (800 ml.), concentrated hydrochloric acid (72 ml.) was added and all urobilin hydrochloride was extracted into chloroform (500 ml.). The solution was dried (Na_2SO_4) for a short time and filtered. Spectroscopic examination of the chloroform solution showed the presence of 15 mg. of urobilin of $[\alpha]_D$ +4900° in $CHCl_3$ (pigment assumed to have the same extinction coefficient as d-urobilin hydrochloride). The crude urobilin precipitated from concentrated chloroform solution by the addition of cold dry acetone was recrystallised twice from methanol–ethyl acetate (yield 12 mg., dried at 35° *in vacuo* over P_2O_5). The residue given by evaporation of the mother-liquors from the precipitation and crystallisation of the above product was dissolved in saturated sodium acetate solution (4 ml.) and brought on to a column of alumina in water. Elution with water removed an orange band containing a further 0·6 mg. of urobilin, leaving all violet pigment at the head of the column (total yield, 12% of original urobilin). Comparable amounts of the hydrochlorides of d-urobilin, stercobilin, and d-urobilin-IXα were submitted for hydrogenation with the following results.

Pigment	Quantity hydrogenated (mg.)	H_2 absorbed (ml. at N.T.P.)	C:C present	C:C indicated
d-Urobilin	11·76	0·841	2	2
Stercobilin	12·23	0·447	1	1
d-Urobilin-IXα	11·33	0·416	?	1

Two further experiments afforded d-urobilin-IXα.

(*a*) d-Urobilin hydrochloride (55·3 mg.: $[\alpha]_D$ +4220° in $CHCl_3$), reduced catalytically in acetic acid and allowed to reoxidise spontaneously, gave 6·9 mg. (12%) of recovered urobilin.

The chloroform solution had $\lambda_{max.}$ 499 mμ. The methanol solution had $\lambda_{max.}$ 492 and 365 mμ, intensity at the former being increased about three-fold on addition of hydrochloric acid. The crystalline hydrochloride had $[\alpha]_D$ 4250° in $CHCl_3$. The mother-liquors contained violet pigment with $\lambda_{max.}$ at 560—570 mμ.

(*b*) The hydrochloride (50 mg.; $[\alpha]_D$ +4700° in $CHCl_3$), reduced in methanol and reoxidised with iodine, gave 16·9 mg. (34%, estimated spectroscopically) of recovered urobilin of which 5·6 mg. (10·4%) were isolated as the crystalline hydrochloride of $[\alpha]_D$ +3200° in $CHCl_3$).

Racemisation of d-Urobilin.—To d-urobilin hydrochloride (50 mg.; $[\alpha]_D$ +4400° in $CHCl_3$) in water (4 ml.) 2·5N-sodium hydroxide (4 ml.) was added. After 45 min. under hydrogen the solution was diluted to 200 ml. and acidified with 2·5N-hydrochloric acid (8 ml.). All orange pigment was then removed by chloroform extraction, leaving the aqueous solution slightly violet. The chloroform extract, dried by filtration and diluted to 250 ml., had $\lambda_{max.}$ at 499 mμ and, $E^{1\%}_{1cm.}$ being assumed equal to that of d-urobilin, appeared to contain 31 mg. of urobilin. This solution was optically inactive (for $[\alpha]_D$ +4000° in $CHCl_3$ the theoretical rotation would be 1°). Crystalline racemic urobilin was obtained by precipitation of the crude pigment in acetone and crystallisation twice from chloroform and once from methanol–ethyl acetate (yield, 14 mg. after drying at 28° over P_2O_5 in a vacuum).

The residue left on evaporation of the mother-liquors was dissolved in saturated sodium acetate solution (4 ml.) and brought on to a column of alumina in water. Elution with water separated a yellow orange band which contained a further 3 mg. of racemic urobilin. Examination of concentrated solutions of either of the two fractions failed to reveal any optical activity.

14·94 mg. of the product absorbed 1·05 ml. (N.T.P.) of hydrogen, the second mol. more slowly (theor. for 2 C:C, 1·07 ml.).

Production of Biliviolinoid Pigments by the Isomerisation and Oxidation of d-Urobilin.—(a) *Oxidation.* d-Urobilin hydrochloride (2·5 mg.; $[\alpha]_D$ +4390° in $CHCl_3$) and a 20% ferric chloride solution in 36% hydrochloric acid (0·5 ml.) in methanol (5 ml.) were boiled for 15 min., diluted with water (25 ml.), rendered neutral to Congo-red by saturated sodium acetate solution (4 ml.), and extracted with ether (150 ml.). Unoxidised urobilin was removed from the ethereal solution by water (8 × 5 ml.), these washings being added to the original aqueous solution. Most of the violet pigment was extracted from the ethereal solution, with considerable deepening of colour, by 2·8N-hydrochloric acid (12 × 5 ml.). The acid solution, diluted to 100 ml. with 2·8N-hydrochloric acid, had $\lambda_{max.}$ at 560—570 mμ (optical density 0·54). Concentrated hydrochloric acid (5 ml.) was added to the original aqueous solution, and urobilin was extracted into chloroform (2 × 50 ml.); spectroscopic examination of this extract showed the presence of 0·7 mg. (30%) of urobilin which, again treated as above, underwent 70% oxidation to violinoid pigments. Violet pigments from the second oxidation in chloroform (20 ml.) showed absorption maxima at 564 mμ (optical density 1·0) with a shoulder at 585—605 (optical density 0·90 at 595 mμ) and 500 mμ (optical density 0·64). The residue left on evaporation of the chloroform solution, dissolved in saturated ethanolic zinc acetate (30 ml.), had absorption maxima at 630 (optical density 0·85), 580 (optical density 0·41) and 510 mμ (optical density 0·33). Addition of 1 drop of 1% ethanolic iodine caused intensification of the maximum at 510 mμ (optical density, 1·16) and almost complete disappearance of the maxima at 580 and 630 mμ (optical density 0·06 at both).

The biliviolinoid pigments obtained by similar oxidation of 5·3 mg. of d-urobilin hydrochloride were eluted from talc with chloroform–ether (2 : 1 v/v). From the main violet band a minor green band partially separated. That portion of the chromatogram containing pure green pigment was removed and the pigment was washed out into chloroform–methanol (1 : 1 v/v). Impure violet pigment was removed from the rest of the column in the same way; the solution was evaporated, and the pigment was dissolved in chloroform–ether (1 : 1 v/v; 2 ml.), and was eluted with the same solvent through a column of magnesium oxide. Some violet and green pigments remained, in separate zones, at the head of the column. A violet band migrated and separated into a (lower) reddish-violet band and a (minor) blue band. A chloroform solution of the pure green pigment showed a broad absorption maximum at 610—670 mμ, the curve being similar to that of glaucobilin in the same solvent but with enhanced absorption at 640—680 mμ. The zinc complex salt, oxidised with ethanolic iodine, showed maxima at 620—625, 575, and 510 mμ. Glaucobilin, dihydrobiliverdin, and biliverdin, treated similarly, gave solutions with the last two maxima at the same position and with the first band at 625, 630—635, and 630—635 mμ, respectively. A chloroform solution of the violet

XUM

pigment showed an indistinct maximum at 560—575 mμ with a pronounced shoulder at 590—610 mμ. The latter characteristic disappeared when the solution was washed with water, the absorption curve then showing a fairly broad maximum at about 560 mμ.

(b) *Isomerisation.* d-Urobilin hydrochloride (5·3 mg.; $[\alpha]_D$ +4390° in $CHCl_3$) in methanol (5 ml.) was treated with 2N-sodium hydroxide (1 ml.) and boiled for 18 min. in an atmosphere of hydrogen. To the cooled solution water (25 ml.), saturated sodium acetate solution (4 ml.), and acetic acid (10 ml.) were added. There was a change of colour from brown to violet and all pigment was extracted into ether (4 × 50 ml.). The amber aqueous solution then contained 0·7 mg. of residual urobilin. Extraction of the ethereal solution with water (16 × 5 ml.) removed a reddish-violet pigment, the solution having $\lambda_{max.}$ 555—558 mμ (unchanged on acidification). Pigment remaining in the ether was extracted with 2·8N-hydrochloric acid (23 × 5 ml.) with change of colour from reddish-violet to pure violet. The two pigment fractions were extracted from aqueous solution into chloroform (70 ml. in each case); the chloroform solutions were washed with water (10 ml.), dried by filtration, and diluted to 100 ml. The chloroform solution of the pigment initially extracted into hydrochloric acid showed absorption maxima at 573—575 mμ. Both chloroform solutions showed slight maxima at 499—500 mμ, due to the presence of a little urobilin; they were united and evaporated to dryness. The residual pigments were dissolved in saturated sodium acetate solution (4 ml.) containing a little acetic acid, diluted with water (25 ml.), and extracted with ether (4 × 50 ml.). The ethereal solution was washed free from urobilin with water (5 × 10 ml.), and all violet pigment was extracted (with deepening of colour) into 2·8N-hydrochloric acid (20 × 5 ml.). The pigment was extracted from acid solution into chloroform (80 ml.). The chloroform solution was washed with water (20 ml.) and dried by filtration; it then had absorption max. only at 577 mμ. A concentrated solution of the zinc complex salt in ethanol showed, after oxidation with iodine, an indistinct and weak maximum at 618—620 mμ.

Other Isomerisation Experiments giving Biliviolinoid Pigments.—(*a*) d-Urobilin hydrochloride (2 mg.) in methanol (7 ml.) containing a few crystals of sodium sulphite was warmed, under hydrogen, at 60° for 5 min. with piperidine (2 ml.), 2·5N-sodium hydroxide (2·0 ml.), or butan-1-olic potassium *tert.*-butoxide (2% of potassium; 0·5 ml.). Addition of excess of acetic acid to the cooled solution produced a brilliant violet colour. No colour developed in solutions treated similarly but without the addition of base.

(*b*) To d-urobilin hydrochloride (20 mg.; $[\alpha]_D$ +4300° in $CHCl_3$) in methanol (20 ml.) under hydrogen 2N-sodium hydroxide solution (4 ml.) was added. The solution was heated under hydrogen at 66° for 18 min., gradually deepening in colour, finally to violet; this colour persisted on dilution to 200 ml. and was intensified on addition of acetic acid (5 ml.). Most pigment was extracted from the acid solution by ether (350 ml.) and was re-extracted from ether into water. Small quantities of pigments remaining in the original aqueous and ethereal solutions were extracted into chloroform (116 ml.) [$\lambda_{max.}$ 499 mμ (optical density, *D* 1·62), 570 mμ (*D* 0·21)] and 10% hydrochloric acid respectively. The pigments in 10% hydrochloric acid were extracted into chloroform (174 ml.) [$\lambda_{max.}$ 505 (*D* 0·34), 570 (*D* 0·29); $\lambda_{min.}$ 535 mμ (*D* 0·21)]. The water-soluble pigments extracted from ether solution were extracted into chloroform (230 ml.) [$\lambda_{max.}$ 505 (*D* 0·85), 720 (*D* 0·40); $\lambda_{min.}$ 555 mμ (*D* 0·38)]. After extraction with 10% hydrochloric acid the ethereal solution was pale green but slowly became violet; the pigment was extracted into 10% hydrochloric acid (again leaving a solution of labile green pigments), and the pigment was extracted from the acid solution into chloroform (64 ml.) [$\lambda_{max.}$ 560—570 mμ (*D* 0·17)].

(*c*) d-Urobilin (16·3 mg.; $[\alpha]_D$ +4320° in $CHCl_3$) in freshly distilled, peroxide-free tetrahydrofuran (5 ml.) was boiled with lithium aluminium hydride (100 mg.) for 1½ hr., becoming violet. After being kept overnight (under hydrogen) excess of hydride was destroyed by dilute hydrochloric acid, the solution diluted with water (300 ml.), and concentrated hydrochloric acid (10 ml.) added. Most of the pigment was extracted into chloroform (400 ml.); the chloroform solution was evaporated to dryness and the residue was dissolved in 10% potassium acetate solution (130 ml.). The aqueous solution was extracted with ether (200 ml.) which removed a small quantity of violet pigment. Re-extraction of the ethereal solution with 1·5N-hydrochloric acid removed the violet pigment, leaving the ethereal solution greenish-yellow. The ether was evaporated to provide a green residue which gave a solution in chloroform (100 ml.) with $\lambda_{max.}$ 410 mμ (*D* 0·143). Pigment remaining in the aqueous solution after the ether-extraction was extracted into chloroform (500 ml.) giving a reddish solution with

$\lambda_{max.}$ 570 mμ (*D* 1·066). The aqueous solution (140 ml.), now of urobilinoid colour with $\lambda_{max.}$ 492 mμ (*D* 0·65), was treated with concentrated hydrochloric acid (20 ml.). All urobilin was then extracted into chloroform (150 ml.); the resulting solution had $\lambda_{max.}$ 499 mμ (*D* 0·540; representing 600 μg. of urobilin).

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Department of Chemical Pathology,
King's College Hospital Medical School, London, S.E.5. [*Received, March 11th*, 1958.]

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628. *The Vapour Pressure of Anhydrous Copper Nitrate, and its Molecular Weight in the Vapour State.*

By C. C. Addison and B. J. Hathaway.

Reaction of copper metal with a mixture of dinitrogen tetroxide and ethyl acetate yields the compound $Cu(NO_3)_2,N_2O_4$, which loses dinitrogen tetroxide to give anhydrous copper nitrate at 85°. When heated to higher temperatures *in vacuo*, the anhydrous salt sublimes, and condenses as deep blue-green crystals. Vapour pressures have been recorded up to 226°, at which temperature the vapour becomes unstable. The heat of sublimation is 15·6 kcal./mole. Molecular-weight measurements on the vapour show it to be monomeric. Attempts to determine the molecular weight by a transport method were unsuccessful, but indicated that the decomposition temperature of the vapour is lowered in the presence of other gases. Possible structures for the copper nitrate molecule are discussed.

Brief reference has recently been made to the volatility of anhydrous copper nitrate.[1] Vapour pressures over a temperature range and molecular weights in the vapour state have now been determined. References to the preparation of anhydrous cupric nitrate are conflicting. Thus, it is stated to be unknown,[2] but also that it separates as a white or pale green crystalline meal from solutions rich in nitric acid.[3] Ditti [4] claims to have prepared the compound by dissolving copper nitrate hydrate (which had been heated until red fumes were evolved) in hot anhydrous nitric acid and allowing it to cool, but repetition failed to yield an entirely anhydrous product. Guntz and Martin [5a] studied the reaction of copper metal with silver nitrate dissolved in an anhydrous solvent (acetone, phenyl cyanide or liquid ammonia). They considered that a cupric salt was produced in these solvents, though Morgan [6] has shown that displacement of silver from a silver nitrate solution in acetonitrile gives the cuprous salt. Complete replacement occurred but evaporation of the resulting solution gave a copper nitrate–solvent addition compound of variable composition. Efforts to remove this solvent resulted in thermal decomposition of the nitrate. Guntz and Martin also refluxed a mixture of hydrated copper nitrate (from which most of the water had been removed by heating) with dinitrogen pentoxide in anhydrous nitric acid. The analysis of the pale blue solid which separated corresponded with anhydrous copper nitrate.[5b] Reaction of copper oxide with acetyl nitrate was used by Chrétien and Boh [7] to prepare the anhydrous nitrate, again as a pale blue powder.

[1] Addison and Hathaway, *Proc. Chem. Soc.*, 1957, 19.
[2] Sidgwick, "The Chemical Elements and their Compounds," Oxford Univ. Press, 1950, p. 155.
[3] Remy, "Treatise on Inorganic Chemistry," Elsevier Publishing Co., New York, 1956, Vol. II, p. 388.
[4] Ditti, *Ann. Chim. Phys.*, 1879, **18**, 320; *Compt. rend.*, 1879, **89**, 576.
[5] Guntz and Martin, (*a*) *Bull. Soc. chim. France*, 1910, **7**, 313; (*b*) 1909, **5**, 1004.
[6] Morgan, *J.*, 1923, **123**, 2901.
[7] Chrétien and Boh, *Compt. rend.*, 1945, **220**, 822; Boh, *Ann. Chim. France*, 1945, **20**, 421.

XUM

Ferraro and Gibson [8] heated dinitrogen tetroxide with freshly prepared cupric oxide in a sealed tube at 87° and 14·7 atm. pressure for 7·5 hours. This gave a jade-green microcrystalline solid, to which the formula $Cu(NO_3)_2,2NO_2$ was assigned, which decomposed at 90°—140°/10^{-5} mm. to anhydrous copper nitrate, but the volatility of the latter was not observed.

The present work provides an alternative interpretation of some experiments by Neumann and Sonntag,[9] who treated copper oxide with gaseous dinitrogen tetroxide for some days at 25°, obtaining a brown-black microcrystalline product (termed anhydrous copper nitrate) which decomposed above 80° to a product regarded as a basic nitrate. It is now known that the compound $Cu(NO_3)_2,N_2O_4$ has a dissociation vapour pressure of dinitrogen tetroxide of 1 atm. at 83·5°, and that copper nitrate does not decompose to a basic nitrate at this temperature. Neumann and Sonntag did not give full analyses of their products, and it seems probable that their experiments were concerned with the preparation and decomposition of the addition compound $Cu(NO_3)_2,N_2O_4$.

The method now given is believed to be the simplest for the preparation of anhydrous copper nitrate. By sublimation of the amorphous powder so obtained, the nitrate can be obtained as large blue-green crystals.

Experimental

Preparation and Sublimation of Anhydrous Copper Nitrate.—A freshly abraded strip (10 g.) of pure copper was added to a mixture of 20 ml. of dinitrogen tetroxide with 20 ml. of dried ethyl acetate in a 17 × 3 cm. glass tube closed by a B24 ground joint and phosphoric oxide guard tube. Nitric oxide was evolved vigorously and the colour of the solution changed from red to dark green. Reaction was complete after 4 hr. at room temperature. Unchanged copper was then removed, the solution (which increased appreciably in viscosity during reaction) was filtered in a closed system, and excess of liquid dinitrogen tetroxide added until precipitation of $Cu(NO_3)_2,N_2O_4$ was complete. This was filtered off, washed with liquid dinitrogen tetroxide, and transferred to a 17 × 3 cm. tube where the excess of tetroxide was removed under a vacuum at 0°.

The thermal decomposition $Cu(NO_3)_2,N_2O_4 \longrightarrow Cu(NO_3)_2 + N_2O_4$ was effected by immersing the tube in an oil bath, and maintaining the vacuum while raising the temperature slowly to 120°; anhydrous copper nitrate remains as a pale blue amorphous powder. A 0·5 cm. layer of cleaned and dried glass wool was then packed on the surface of the copper nitrate in the bottom of the tube, which was re-evacuated and arranged so that the oil level in the bath was about 3 cm. above the surface of the glass wool. The bath temperature was raised to 200°, whereupon copper nitrate rapidly sublimed, the sublimate collecting on the walls of the tube, leaving only about 0·3 cm. of clear glass above the oil level. The sublimation of 10 g. of copper nitrate was complete in about 4 hr. A small amount of dark olive-green powder (less than 5% of the starting material) remained. The sublimate was a deep blue-green crystalline mass, but if the sublimation was arrested early long needles could be isolated [Found: Cu, 33·83; N, 14·85. $Cu(NO_3)_2$ requires Cu, 33·85; N, 14·93%]. Slower sublimation is possible at much lower temperatures; thus at 130°, 100 mg. quantities have been collected in 2—3 hr., and smaller quantities at as low as 100°. Anhydrous copper nitrate is very deliquescent, and all manipulations are carried out in a dry-box.

Melting Point.—When a sealed capillary was plunged into a bath at 255° the sample shrunk with signs of wetting, and at 256° the solid melted to a green liquid. In a similar experiment at 260°, the sample melted to an emerald-green liquid which almost immediately decomposed with evolution of bubbles of gas. The m. p. is therefore 255—256°. The nitrates of the alkali metals and of silver have lower m. p.s than the chlorides and the above value is consistent with this pattern (cf. $CuCl_2$, m. p. 498°).

Vapour Pressures.—Preliminary investigations indicated that a satisfactory technique must allow for the following points: (*a*) There appears to be no fluid suitable for use in a manometer. If mercury was used, a yellow solid was formed on the walls of the vessel containing

[8] Ferraro and Gibson, *J. Amer. Chem. Soc.*, 1953, **75**, 5747.
[9] Neumann and Sonntag, *Z. Electrochem.*, 1935, **41**, 611.

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copper nitrate, produced by a gas-phase reaction with mercury vapour. Of the low-vapour-pressure oils, Silicone fluid M.S. 550 and Apiezon high vacuum grease L (which is liquid at the temperatures used) both showed signs of chemical attack. An all-glass system incorporating a spiral gauge was therefore used. (*b*) On being heated, solid copper nitrate evolves small quantities of decomposition products ($NO_2 + O_2$) as well as copper nitrate molecules. The vapour pressure of the latter is of the order of a few mm. Hg; this is independent of the volume of the containing vessel, whereas the pressure set up by decomposition products from a given quantity of solid is decreased as the containing vessel becomes larger. The vessel must therefore be big enough for the pressure due to copper nitrate vapour to be readily identified. (*c*) The state of the surface of solid nitrate has a critical influence. The rate of development of pressure at a given temperature decreases with time, even though the proportion of the solid decomposing is almost negligible. It appears that decomposition occurs first at the surface of the solid, producing a layer of decomposition product (copper oxide or a basic nitrate) which acts as a barrier to vaporisation of copper nitrate molecules. Vapour-pressure measurements were therefore carried out only on freshly sublimed solid. (*d*) The whole of the vessel containing the vapour must be at the temperature of measurement, otherwise copper nitrate will immediately condense on any cool spot. (*e*) Copper nitrate will vaporise into a vacuum to give

FIG. 1.

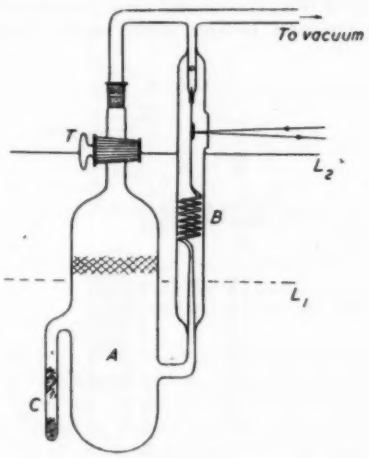
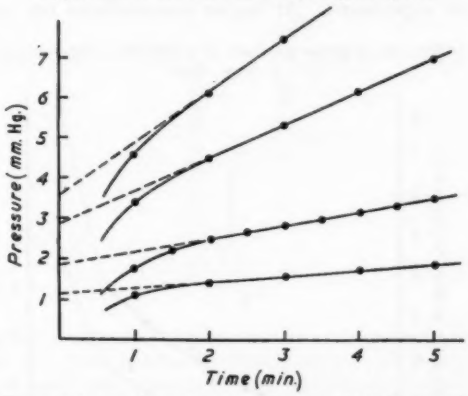


FIG. 2. *Rate of development of pressure when anhydrous copper nitrate is heated in a large vapour space.*



Temperatures, from top to bottom, 222·6°, 215·2°, 202·0°, 189·5°.

its full equilibrium vapour pressure, but not in presence of other gases (see molecular-weight measurements by the transport method below).

The apparatus used is shown in Fig. 1. To a vessel *A* (520 ml.) was attached a glass-spiral gauge *B* (sensitivity 90° deflection per atm.). The spiral gauges were kindly prepared by Mr. S. Kettle of the Inorganic Laboratories, Cambridge; such gauges are undamaged by sudden temperature changes from room temperature to 250°. Before the vapour-pressure measurements, the gauge *B* was calibrated to read pressure in *A* against vacuum in *B* (*i.e.*, outside the spiral), and the change in the zero (vacuum–vacuum) reading of the spiral with temperature was determined by immersing the empty apparatus in the bath at various temperatures.

Sublimed copper nitrate was placed in the bottom of tube *C*, followed by a plug of glass wool, and *C* then sealed into *A* as shown. The apparatus was degassed by flaming under vacuum, and placed in an oil-bath at 200° so that the oil was at level L_1. The vacuum being maintained, copper nitrate sublimed from *C* and condensed as a band of crystals round the inner walls of *A* a little above L_1. This provided a large surface area of fresh copper nitrate for subsequent ready vaporisation. The apparatus was then withdrawn from the oil-bath, the side arm *C* drawn off, and the apparatus and optical system mounted rigidly. The oil-bath (controlled to within $\pm 0{\cdot}1°$) was then raised round the apparatus to the oil level L_2. It was essential that tap *T* should be partly immersed, to prevent condensation of copper nitrate on

the barrel. When T was partly immersed, the optical window in B was just above the oil surface.

After T was closed the pressure in A was recorded at ½ min. intervals. The type of pressure–time curve obtained is shown in Fig. 2. Each curve falls into two sections, an initial rapid rise in pressure representing vaporisation of copper nitrate, followed by a slower linear increase due to decomposition of the solid. Extrapolation of this line (which was straight for at least 10 minutes' heating) to zero time gives the true vapour pressure of copper nitrate. It is therefore important that the time scale should be correctly chosen. A finite time is required for the heat from the oil-bath to pass through the walls of A and to bring the copper nitrate to the temperature of the bath. When a measurement was started, the bath was therefore raised round the apparatus with T open and the whole apparatus under a vacuum. T was kept open until the copper nitrate reached the bath temperature, which was indicated by the appearance of copper nitrate crystals in its barrel. T was then closed and this time taken as zero.

This technique being used, values obtained are given in Table 1.

TABLE 1. *Vapour pressure of anhydrous copper nitrate.*

Temp. (°)	157·0	172·8	186·4	189·5	202·0	215·2	222·6
Vapour pressure (mm. Hg)	0·32	0·59	0·99	1·15	1·87	2·84	3·59

The pressure values quoted are believed to be accurate to ±0·02 mm. Hg.

Vapour-phase Decomposition.—Below 225°, the walls of A (Fig. 1) remained clear throughout an experiment. At higher temperatures the vapour pressures became much higher than

FIG. 3. *Vapour pressure of anhydrous copper nitrate (mm. Hg).*

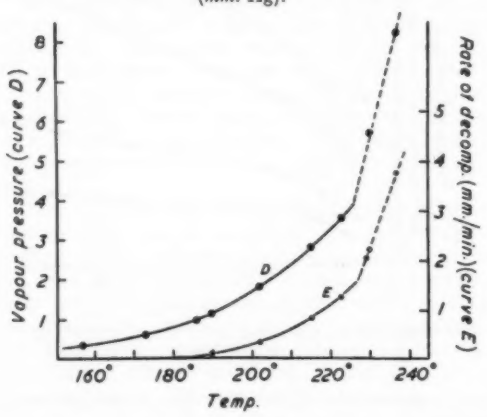
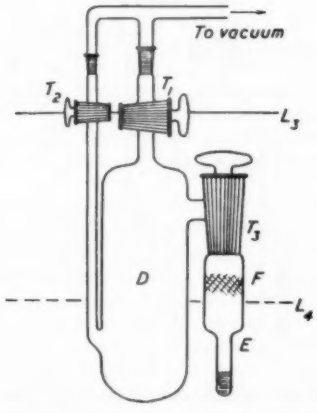


FIG. 4.



expected from extrapolation of the values in Table 1, and the walls were rapidly covered with a fine, dark deposit, indicating decomposition of the vapour. The vapour pressure–temperature curve (D, Fig. 3) shows a sharp break; the graph of log p against $1/T$ is straight over the temperature range at which the vapour is stable, and the break in this graph at the decomposition temperature shows that the vapour begins to decompose very sharply at 226°. The gradients of the straight portions of the pressure–time curves (Fig. 2), obtained by use of similar quantities of solid copper nitrate, are also plotted against temperature in Fig. 3 (curve E) and again show a break at 226°. The stability of copper nitrate vapour is therefore greater than that of the solid; in the absence of high pressure of other gases (see below) there is no evidence for decomposition of the vapour below 226°, whereas the decomposition of the solid is measurable even below 190° (Fig. 2). The higher pressures and gradients above 226° (Fig. 3) result from the fact that the oxygen–nitrogen dioxide mixture responsible is now produced by decomposition of copper nitrate in both the solid and the vapour state.

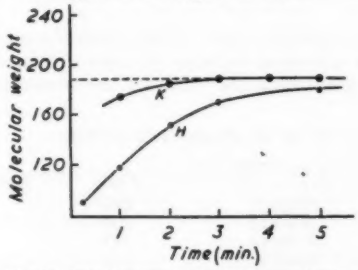
By extrapolation of the log p–$1/T$ graph, the vapour pressure of copper nitrate at its m. p. (256°) would be 8·7 mm. Hg if the vapour did not decompose.

Molecular Weight in the Vapour Phase.—This determination involved measurement of the

quantity of copper nitrate present in a given volume of vapour at a known temperature. The apparatus (Fig. 4) was designed so that when equilibrium pressure was established, the solid could be isolated from the vapour. Taps T_1 and T_2 were at the same level so that each could lie in the surface (L_3) of the oil. A side tube F was attached to vessel D (capacity 740 ml.) through a hollow-barrelled 10 mm. bore tap T_3 arranged so that its barrel would lie below L_3. The apparatus was flamed under vacuum, and a narrow tube containing copper nitrate covered by a glass wool plug sealed to tube F at E as shown. With all taps open to vacuum, the oil-bath at 200° was raised to level L_4, and copper nitrate sublimed into F. The oil level was then raised to L_3, with T_1 and T_2 open and T_3 closed. The temperature of the bath was adjusted to 217°, and the apparatus allowed 10 min. to achieve this temperature. T_1 was then closed and T_3 opened to allow copper nitrate vapour to pass into D. T_3 was kept open until copper nitrate was seen to condense in this tap (which usually occurred 6—7 sec. after opening T_3); T_3 was then closed. This step ensured the removal from D of as much as possible of the gaseous decomposition products which had accumulated in F, and also confirmed the passage of copper nitrate vapour from F into D.

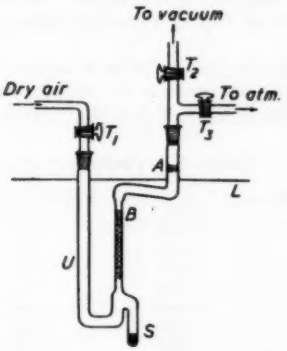
T_3 was then closed and T_1 opened, thus drawing the vapour from D though the barrel of T_1, where it condensed. To increase the amount of copper nitrate available for analysis, the

FIG. 5. *Molecular weight of anhydrous copper nitrate vapour at 217°.*



The broken line represents the molecular weight of the monomer (187·6).

FIG. 6.



above process could be repeated several times, thus accumulating an amount of copper nitrate in T_1 equivalent to a multiple of the volume of D. Since T_3 must be closed before T_1 is opened, it was necessary to ensure that T_3 remained open long enough for the equilibrium vapour pressure of copper nitrate to be established in D. A series of experiments were therefore carried out which were identical except that T_3 was kept open for different periods. The results are given in Table 2 (row 4), where the Time is that allowed and the Weight is that of copper nitrate condensed per evacuation of the vessel (calculated from the weight of copper–ethylenediamine–mercury iodide complex).

TABLE 2. *Condensation of copper nitrate from vapour.*

Time (min.)	0·25	1·0	2·0	3·0	4·0	5·0	5·0	5·0
Temp.	217°	217°	217°	217°	217°	217°	180°	198°
Weight (g.)								
Apparatus 1 (560 ml.)	0·00489	0·00651	0·00840	0·00932	—	0·00966	—	—
Apparatus 2 (Fig. 4) (740 ml.)	—	0·0125	0·0133	0·0135	0·0134	0·0135	0·0127	0·0131

From each experiment the apparent molecular weight of copper nitrate in the vapour was calculated and the results are shown in Fig. 5 as the curve K. The molecular weight rapidly rises to, and levels off at, the value corresponding to the monomer $Cu(NO_3)_2$, which thus represents the state of this compound as vapour. The results in row 3 (Table 2) and curve H (Fig. 5) were obtained with an apparatus in which a straight-bore tap was used at T_3 (Fig. 4). This interposed a longer tube between F and D, and equilibrium vapour pressure was established more slowly.

This molecular weight is probably independent of temperature. Measurements at 180°

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and 198° (Table 2) gave molecular weights of 175 and 180 respectively. At these temperatures the lower equilibrium pressures may be more slowly attained with the type of apparatus used and this is probably responsible for the slightly lower molecular weights observed.

Molecular Weight by the Transport Method.—The total pressures recorded in the vapour-pressure measurements (Fig. 2) did not normally exceed 10 mm. Hg. Attempts to determine the molecular weight of copper nitrate by the transport method were made primarily to examine the behaviour of copper nitrate vapour in the presence of other gases. Air, thoroughly dried and at atmospheric pressure, was used in the apparatus shown in Fig. 6. Anhydrous copper nitrate was placed in side arm S of the U-tube U, and the tube evacuated through T_2 with T_1 and T_3 closed. An oil-bath at 210—220° was raised round U to level B, whereupon copper nitrate condensed in the outgoing arm of U (5 mm. bore). By gradual lowering of the oil level, this arm was almost filled with crystals for a distance of 5 cm., after which the oil-bath was removed, and dry air admitted to the cool apparatus. The bath was then brought to the desired temperature, and raised round the U-tube to the final level L shown in Fig. 6. The apparatus was allowed 3 min. to attain bath temperature; a very slow stream of dry air was then passed through the apparatus *via* T_1 and T_3. Copper nitrate was transported from the U-tube, and condensed as crystals at point A. Occasionally, needles formed which tended to fall away when the apparatus was moved; the tube below A was therefore bent as shown to form a trap for such crystals. After an experiment, the tube was cut at this trap, and the quantity of copper nitrate transported was determined by analysis. Results are given in Table 3.

From the data in Table 3, and on the assumption that copper nitrate gives the same equilibrium vapour pressure in contact with air as it does in a vacuum, it is possible to calculate molecular weights M (col. 6). These are much lower than the value for the monomer formed

TABLE 3. *Transport of copper nitrate by air at atmospheric pressure.*

Expt. No.	Rate *	Duration of expt. (min.)	$Cu(NO_3)_2$ transported per l. of air	Temp.	M (apparent)
1	0·546	60	0·00982	204°	90
2	1·053	60	0·00810	204	74
3	1·310	60	0·00845	203	77
4	1·469	60	0·00756	204	69
5	2·090	60	0·01020	204	93
6	0·700	60	0·0184	217	112
7	1·500	60	0·0229	217	139
8	2·275	60	0·0210	217	128
9	4·460	30	0·0156	217	95
10	1·87	60	0·0255	220	141
11	1·87	60	0·0272	224	131

* l. of dry air per hr. corrected to 760 mm. at 20°.

in the absence of foreign gases, and the results indicate either that gas–solid equilibrium was not achieved, or that the stability of cupric nitrate vapour is influenced by the presence of other gases. The former is unlikely, since the weight of copper nitrate transported per litre of air does not increase as flow-rate decreases (cf. expts. 1—5 with 6—9); in fact, in some cases the reverse is true (cf. expt. 5 with 4, and 7 with 6). Experiment 9 was carried out for a shorter period to ascertain whether the smaller quantity transported was due to ageing of the copper nitrate surface during vaporisation, but again a low value was obtained.

All the transport experiments were carried out below the temperature (226°) at which copper nitrate vapour has been found to decompose, and in the presence of air at atmospheric pressure the vapour therefore decomposes at lower temperatures. This was supported by examination of that part of the U-tube (Fig. 6) between B and A which is traversed by the vapour. In all cases the internal wall was coated with a very thin dark green film similar in appearance to that formed on the walls of the vapour-pressure vessel (Fig. 1) above 226°. The identity of this copper compound has not yet been established; it is insoluble in water but readily soluble in dilute nitric acid. Copper nitrate vapour probably decomposes in the vapour-phase rather than by a heterogeneous process, the decomposition temperature being determined by the molecular weight, chemical nature, and the pressure of added gases.

The influence of total pressure has been illustrated by use of an apparatus similar to that shown in Fig. 1, except that the vessel A was replaced by a single narrow tube joining tap and

spiral gauge. The internal volume was thereby reduced from 520 ml. to 35 ml., and in this small volume the nitrogen dioxide and oxygen formed by decomposition of the solid nitrate give rise to much higher pressures than those indicated in Fig. 2. Typical pressure–time curves obtained on heating at 220° are shown in Fig. 7. Curve I was obtained on first heating. The apparatus was then evacuated and tap *T* closed, and curve II represents the subsequent development of pressure. Each curve shows a sharp break at about 5 cm. Hg total pressure. The initial part of the curve represents ($NO_2 + O_2$) pressure from solid decomposition, together with the relatively small pressure of stable copper nitrate vapour. The decomposition temperature of the latter falls from the vacuum value of 226° to 220° under 5 cm. Hg pressure;

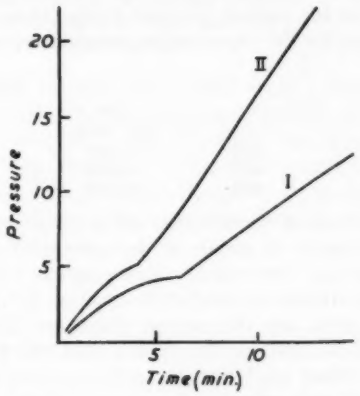
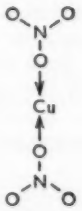


FIG. 7. *Changes of pressure (cm. Hg) when anhydrous copper nitrate is heated at 220° in a small vapour space.*

at higher pressures decomposition occurs *via* copper nitrate vapour also, and is therefore more rapid. These experiments present a unique problem in gas kinetics which we propose to explore more fully.

DISCUSSION

The most remarkable properties of anhydrous copper nitrate are its volatility, its monomeric state in the vapour, and its rich blue colour. These all indicate that a high degree of covalency exists in a molecule which would normally, on the basis of present knowledge, be regarded as fully ionic, and that in anhydrous compounds the nitrate group is capable of a type of bonding not hitherto realised. If we assume that each nitrate ion is bonded to the copper ion in the same manner, there are three possible structures for the molecule.



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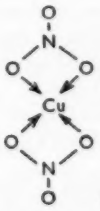

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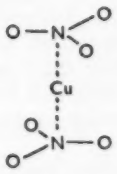


(III)

The unidentate nitrate group (I) is the form usually assumed for nitrato-complexes. However, the nitrate group is generally recognised as a weak ligand in co-ordination complexes, and is readily replaced by water. It seems inconsistent, then, that a metal–nitrate bond which is sufficiently strong to enable the molecule to exist as a monomer in the vapour phase should be of this form. There is no doubt however that covalency exists; from the infrared spectrum of nitrato-complexes it is possible to distinguish a covalent from an ionic nitrate group,[10] though it is not yet possible by this means to

[10] Gatehouse, Livingstone, and Nyholm, *J.*, 1957, 4222.

determine unequivocally the precise manner in which the NO_3 group is bonded. The infrared spectrum of solid copper nitrate shows it to be pronouncedly covalent.[11]

The nitrate group does not usually enter co-ordination complexes as a bidentate ligand (II), although the CO_3^{2-} group readily does so. Crystallographic data [12] indicate that in the complex $[UO_2(NO_3)_3]^-$ the uranyl group is normal to a plane in which lies a ring of six oxygen atoms (from three bidentate nitrate ions) surrounding the uranium atom. It has also been suggested that the ruthenium complex $Ru_2N_6O_{15}$ may contain bidentate groups.[13] Structure (II) is therefore possible, but is less attractive than structure (III) which most readily explains the thermal properties of the compound.

From the vapour pressure–temperature relation (Fig. 3) the relevant thermodynamic functions for the vaporisation process have been calculated at three temperatures (Table 4).

TABLE 4.

T (°K)	ΔH (cal./mole)	ΔG (cal./mole)	ΔS [cal./(mole degree)]
453	15,600	6200	20·8
473	15,600	5730	20·9
493	15,600	5330	20·8

The heat of vaporisation ΔH is surprisingly low, and is of the same order as values for the carbonyls of metals of the chromium group, and some metal *cyclo*pentadienyl compounds (*e.g.*, ferrocene). This suggests that intermolecular forces are small, which led us to postulate the sandwich structure (III). It is possible, of course, that the structures in the solid and the vapour phase are different; the infrared spectrum of the vapour contains at least one absorption band which has not been observed for solid copper nitrate or any other solid nitrate, and is at present unassigned.[11] Structure (III) is therefore proposed primarily for the vapour phase, where an isolated molecule free from lattice forces can more readily attain molecular symmetry. The broken lines do not carry any implication regarding the number of electrons used in bonding, or their location, but they emphasise the fact that the three oxygen atoms in the co-ordinated nitrate ion are equivalent. Covalency may result from overlap of a bonding π-orbital of the nitrate ion with metal *d*-orbitals. The former is centrosymmetrical, which is consistent with sandwich-type bonding.

The structure of solid copper nitrate is now under examination (by Dr. S. C. Wallwork in these laboratories) by *X*-ray crystallography, so that detailed discussion of possible structures is unnecessary at this time. We may comment, however, that structure (III) represents hexaco-ordination of the copper ion by oxygen atoms, but a molecular model indicates Cu–O distances which are too long for strong bonding. Regular octahedral environment of the cupric ion rarely, if ever, occurs.[14] However, a distorted form of structure (III) is obtained if the co-ordination is regarded as square-coplanar (II) and each nitrate ion is then tilted so that the third oxygen atom is above (and below) the plane, giving four short and two long Cu–O bonds. The blue colour of the anhydrous nitrate is consistent with structure (II), or with (III) or its distorted form. It is of interest that the anhydrous carbonate complex $K_2[Cu(CO_3)_2]$ also has an unexpectedly deep blue colour.[15]

It is now known that these unusual features of nitrate-ion bonding are not restricted to the copper compound; anhydrous ferric and mercuric nitrates are also volatile.[16]

THE UNIVERSITY, NOTTINGHAM. [*Received, April 2nd,* 1958.]

[11] Addison and Gatehouse, *Chem. and Ind.*, 1958, **464**.
[12] Hoard and Stroupe, Atomic Energy Project Report, 1943, A, 1229; Jander and Wendt, *Z. anorg. Chem.*, 1949, **258**, 1; Zachariasen, *Acta Cryst.*, 1954, **7**, 795; see also Coulson and Lester, *J.*, 1956, 3650.
[13] Fletcher, "Proceedings of the International Conference on Co-ordination Complexes," Rome 1957, *Ricerca sci.*, 1958, in the press.
[14] Orgel and Dunitz, *Nature*, 1957, **179**, 462.
[15] Reynolds, *J.*, 1898, **73**, 262; Applebey and Lane, *J.*, 1918, **113**, 609.
[16] Addison, Hathaway, and Logan, *Proc. Chem. Soc.*, 1958, 51.

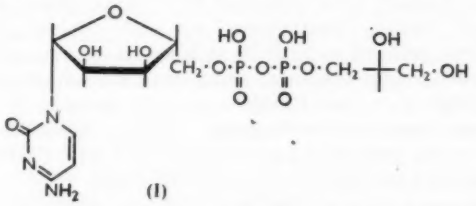
629. *Synthesis of Cytidine Diphosphate Glycerol.*

By J. BADDILEY, J. G. BUCHANAN, and A. R. SANDERSON.

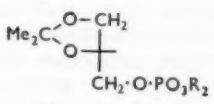
Hydrogenolysis of 2 : 3-*O*-*iso*propylideneglycerol 1-(diphenyl phosphate) (II; R = Ph) at pH 7 gave 2 : 3-*O*-*iso*propylideneglycerol 1-phosphate (II; R = H). Cytidine diphosphate DL-glycerol was prepared from this phosphate and cytidine-5′ phosphate in the presence of di*cyclo*hexylcarbodi-imide, followed by removal of the *iso*propylidene group from the product.

Starting from 1 : 2-*O*-*iso*propylidene-L-glycerol a high yield of CDP-glycerol, identical with the natural compound, was obtained.

CYTIDINE DIPHOSPHATE GLYCEROL (CDP-glycerol) (I) was first isolated from *Lactobacillus arabinosus* [1,2] and is believed to be an intermediate in the enzymic synthesis of polyol phosphate-containing compounds of complex structure.[3] Its structure was determined by both chemical and enzymic methods,[4,5] but shortage of material precluded the elementary analysis of the nucleotide and the isolation of degradation products in sufficient amount for conventional analysis. For these reasons, and more especially for enzymic studies, a synthesis of CDP-glycerol was highly desirable.



(I)



(II)

Of the several methods available for the synthesis of unsymmetrical pyrophosphates, the most promising at the time when this work started was that described by Khorana and Todd,[6] in which the two phosphates are condensed in the presence of a carbodi-imide. For the synthesis of CDP-glycerol, condensation between cytidine-5′ phosphate and α-glycerophosphate or one of its derivatives was envisaged.

Hitherto, the most satisfactory preparation of cytidine-5′ phosphate involved phosphorylation of 2′ : 3′-*O*-*iso*propylidenecytidine with a mixture of phosphoric acid and phosphoric oxide, followed by hydrolysis.[7] In this route, which is based on an earlier synthesis of pyridoxal phosphate,[8] 2′ : 3′-*O*-*iso*propylidenecytidine is obtained in moderate yield from cytidine. A modified synthesis of the nucleotide, starting from the more readily available cytidine sulphate and proceeding through 2′ : 3′-*O*-benzylidenecytidine, is described in this paper. The yield of cytidine-5′ phosphate was 45%, based on cytidine sulphate.

No unsymmetrical pyrophosphate was detected when cytidine-5′ phosphate and α-glycerophosphate were treated with di*cyclo*hexylcarbodi-imide in aqueous pyridine under a variety of conditions. Reaction mixtures, examined by paper chromatography and ion-exchange methods, contained cytidine-5′ phosphate, P^1P^2-dicytidine-5′ pyrophosphate, and the 1 : 2-cyclic phosphate of glycerol. Preferential cyclisation of the

[1] Baddiley and Mathias, *J.*, 1954, 2723.
[2] Baddiley, Buchanan, Carss, Mathias, and Sanderson, *Biochem. J.*, 1956, **64**, 599.
[3] Baddiley, Buchanan, and Greenberg, *ibid.*, 1957, **66**, 51P.
[4] Baddiley, Buchanan, Mathias, and Sanderson, *J.*, 1956, 4186.
[5] Baddiley, Buchanan, and Carss, *J.*, 1957, 1869.
[6] Khorana and Todd, *J.*, 1953, 2257.
[7] Hall and Khorana, *J. Amer. Chem. Soc.*, 1955, **77**, 1871.
[8] Baddiley and Mathias, *J.*, 1952, 2583.

XUM

glycerophosphate is understandable in view of the known ease with which this occurs in the presence of carbodi-imides.[9]

In order to prevent cyclisation of α-glycerophosphate in the above type of reaction it would be necessary to protect at least the 2-position. 2 : 3-*O*-*iso*Propylideneglycerol 1-(diphenyl phosphate) (II; R = Ph) has been prepared[10] from 2 : 3-*O*-*iso*propylideneglycerol in a synthesis of α-glycerophosphate. During the subsequent hydrogenolysis of this neutral ester acidic conditions normally develop, and the *iso*propylidene residue is lost. We have found that hydrogenolysis occurs slowly but smoothly in an acetate buffer at pH 7 to give 2 : 3-*O*-*iso*propylideneglycerol 1-phosphate (II; R = H), isolated in good yield as its barium and *cyclo*hexylammonium salts.

The successful use of the *O*-*iso*propylideneglycerol derivative in a synthesis of CDP-glycerol would depend upon removal of the *iso*propylidene residue after condensation of the phosphate (II; R = H) with cytidine-5′ phosphate. The natural glycerol nucleotide is known to be labile towards acids, so optimum conditions for the removal of the protecting group were examined. Hydrolysis of the *iso*propylidene group from the phosphate (II; R = H) was complete after 4 hr. at pH 2 at room temperature. Little or no hydrolysis of CDP-glycerol would be expected under these mild conditions.

Cytidine-5′ phosphate, an excess of the phosphate (II; R = H), and di*cyclo*hexylcarbodi-imide reacted smoothly in aqueous pyridine. After hydrolysis of the *iso*propylidene residue at pH 2 the products were separated by concave gradient elution chromatography on Dowex-1 resin, elution being carried out with calcium chloride.[11] The main products were a compound believed to be P^1P^2-diglycerol 1-pyrophosphate and CDP-glycerol. Some P^1P^2-dicytidine-5′ pyrophosphate and a small amount of unchanged cytidine-5′ phosphate were also detected. The CDP-glycerol was isolated as its calcium salt from the appropriate fractions from the ion-exchange column. However, during isolation considerable hydrolysis of the pyrophosphate occurred and pure CDP-glycerol was not obtained. The reason for this hydrolysis is under investigation.

In the above synthesis DL-*O*-*iso*propylideneglycerol was used and, unless asymmetric synthesis had occurred, the product would be a mixture of comparable amounts of cytidine diphosphate D-glycerol and cytidine diphosphate L-glycerol. The natural compound contains an L-α-glycerophosphate residue and although this difference between synthetic and natural materials is probably unimportant in connection with the comparison of their chemical properties it would become apparent in enzymic studies. The enantiomorph of *iso*propylideneglycerol which would be required for a synthesis of CDP-glycerol of correct configuration is 1 : 2-*O*-*iso*propylidene-L-glycerol (equivalent to 2 : 3-*O*-*iso*propylidene-D-glycerol). This is obtained by oxidation of 1 : 2-5 : 6-di-*O*-*iso*propylidene-D-mannitol with lead tetra-acetate, followed by catalytic reduction of the resulting *O*-*iso*propylideneglyceraldehyde. This route has been used successfully in a well-known synthesis of L-α-glycerophosphate.[12] We have converted the optically active *O*-*iso*propylideneglycerol into its phosphate and used this in a synthesis of CDP-glycerol by the method described above. The products were separated by ion-exchange chromatography and the nucleotide was isolated as its lithium salt. A little decomposition to cytidine-5′ phosphate and glycerol 1 : 2-(hydrogen phosphate) was always observed. This is consistent with our earlier observation that all CDP-glycerol preparations from natural sources contained detectable amounts of cytidine-5′ phosphate.

In view of the lack of an enzymic test for CDP-glycerol, particularly careful comparison of the chemical behaviour of synthetic and natural products was necessary. They were indistinguishable on paper chromatography, and the synthetic compound yielded cytidine-5′ phosphate and a mixture of α- and β-glycerophosphates on acid hydrolysis. With hot

[9] Dekker and Khorana, *J. Amer. Chem. Soc.*, 1954, **76**, 3522; Khorana, Tener, Wright, and Moffatt, *ibid.*, 1957, **79**, 430.
[10] Brigl and Müller, *Ber.*, 1939, **72**, 2121.
[11] Pontis and Blumsom, *Biochim. Biophys. Acta*, 1958, **27**, 618.
[12] Baer, *Biochem. Preps.*, **2**, 31.

ammonia the products were cytidine-5′ phosphate and the 1 : 2-cyclic phosphate of glycerol. *Crotalus atrox* venom hydrolysed it to cytidine, α-glycerophosphate, and inorganic phosphate. These transformations are also characteristic of CDP-glycerol isolated from natural sources.[4]

Experimental

2′ : 3′-O-*Benzylidenecytidine*.—Cytidine sulphate (14·0 g.; dried for 4 hr. at 100°/0·1 mm.) was suspended in freshly distilled benzaldehyde (100 c.c.). Dry hydrogen chloride was passed through the rapidly stirred suspension, moisture being excluded. After 3 hr. the mixture was poured into dry ether (800 c.c.), and the resulting suspension was shaken with saturated sodium carbonate solution (150 c.c.). Benzylidenecytidine was filtered off and washed with small portions of iced water (3 × 15 c.c.). Recrystallisation from hot water gave a product (13·4 g., 85%) with m. p. 194—196°. Gulland and Smith [13] give m. p. 193—195°.

Cytidine-5′ Phosphate.—2′ : 3′-*O*-Benzylidenecytidine (8·0 g., dried for 8 hr. at 125°/0·1 mm.) was stirred into a warm (60°) mixture of 88% phosphoric acid (40 c.c., 70 g.) and phosphoric oxide (53 g.). The suspension, which was stirred at intervals, was kept at 60° for 2 hr. in a stoppered flask. Water (200 c.c.) was added to the cooled mixture, and the cloudy solution was heated at 100° for 12 min. After being cooled, the solution was extracted with chloroform (4 × 40 c.c.), and the cloudy aqueous layer was neutralised to pH 9·0 with lithium hydroxide solution. Lithium phosphate was centrifuged off and washed with water (3 × 100 c.c.). The combined supernatant solutions were evaporated under reduced pressure to 500 c.c. (a little lithium phosphate was centrifuged off), and passed through a column (4 × 20 cm.) of Dowex-2 resin (chloride form). The column was washed with water (1 l.), which removed a little cytidine (0·4 g.), and cytidine-5′ phosphate was then eluted with 0·005N-hydrochloric acid. The eluate was concentrated under reduced pressure at 30°, then warmed to 80°, and boiling ethanol (250 c.c.) was added. Cytidine-5′ phosphate (4·24 g., 53%) was filtered off and dried. When chromatographed in two solvent systems, the product ran as a single spot, which absorbed ultraviolet light, consumed periodate, and contained phosphate.

We are grateful to Professor G. W. Kenner for unpublished information on the preparation of cytidine-5′ phosphate by a similar route.

2 : 3-O-iso*Propylideneglycerol* 1-*Phosphate*.—2 : 3-*O-iso*Propylideneglycerol 1-(diphenyl phosphate) [10] was dissolved in methanol (90 c.c.) which contained sodium acetate (10·8 g.). Platinum oxide (0·6 g.) was added and the solution was shaken with hydrogen at room temperature and pressure. When absorption of hydrogen had ceased the catalyst was filtered off and washed with methanol (3 × 10 c.c.) and then water (2 × 5 c.c.). A solution of barium acetate (9·3 g.) in water (30 c.c.) was added to the combined filtrate and washings, and a small precipitate of barium phosphate was centrifuged off. Ethanol (1250 c.c.) was added to the supernatant solution. After storage at 0° overnight the barium salt (11·94 g., 100%) was centrifuged off, washed with a little ethanol, and dried *in vacuo*. The cyclo*hexylammonium salt* was prepared by passage of an aqueous solution of the barium salt through a column of the *cyclo*hexylamine form of Dowex-50 resin, followed by evaporation. Recrystallised from alcohol it formed needles, m. p. 198° (Found: N, 6·6; P, 7·6. $C_{18}H_{39}O_6N_2P$ requires N, 6·8; P, 7·6%).

Barium 2 : 3-O-iso*propylidene*-D-*glycerol* 1-*phosphate*, prepared in a similar manner from 2 : 3-*O-iso*propylidene-D-glycerol 1-(diphenyl phosphate) (Found: C, 19·7; H, 3·8; P, 8·5. $C_6H_{11}O_6PBa,H_2O$ requires C, 19·7; H, 3·6; P, 8·5%), had $[\alpha]_D^{17}$ −1·29° (*c* 3·28 in H_2O).

Cytidine Diphosphate Glycerol.—Dowex-50 resin (H^+ form) was converted into the pyridine salt by washing it with pyridine hydrochloride solution, followed by water, until the eluate was free from chloride. To the resin (25 c.c.) was added barium 2 : 3-*O-iso*propylideneglycerol 1-phosphate (5·92 g.) and water (10 c.c.). The resin slurry was stirred until all traces of the barium salt had disappeared and it was then poured on to a small bed (1 × 2 cm.) of Dowex-50 (pyridine form). The resultant column was allowed to drain and the resin was washed several times with portions (6 × 25 c.c.) of water. Dry pyridine (500 c.c.) was added to the combined eluate and washings, and solvent was removed under reduced pressure below 30°. Successive additions of pyridine to the solution were followed by evaporation, until refractive-index measurements on the combined distillates indicated that all the water had been removed. The pyridine solution (*ca.* 12 c.c.) was transferred to a stoppered flask, an additional 13 c.c. of pyridine being added during the transfer. Cytidine-5′ phosphate (0·5 g.), dissolved in pyridine

[13] Gulland and Smith, *J.*, 1948, 1527.

XUM

(15 c.c.) containing water (5 c.c.), was added, followed by aliquot parts (5 c.c.) of a solution of di*cyclo*hexylcarbodi-imide (45 g.) in dry pyridine (20 c.c.). During the addition of the carbodi-imide solution the flask was shaken at room temperature (90 hr.).

Water (10 c.c.) was added to the reaction mixture, and di*cyclo*hexylurea (48 g., 98%) was filtered off and washed with portions (5 × 10 c.c.) of water. The combined filtrate and washings were extracted with chloroform (10 × 100 c.c.), which removed most of the pyridine, and the pH of the aqueous solution was then adjusted to 2·0 with 5% sulphuric acid. After 4 hr. at room temperature the solution was neutralised to pH 7·0 with barium hydroxide solution. Barium sulphate was centrifuged off and washed with water (200 c.c.), and the combined supernatant solutions were passed through a column (1·8 × 50 cm.) of Dowex-1(X2) (200—400 mesh, chloride form). The column was washed with water (250 c.c.) to remove barium ions. Gradient elution was carried out with a solution which was 0·05M in calcium chloride and 0·01N in hydrochloric acid, in the reservoir flask (area of reservoir flask : area of mixing flask = 1 : 3). The rate of elution was 1·8 c.c./min. under a pressure of 1 lb./in.^{2}. Fractions (25 c.c.) were collected and the absorption of each fraction at 280 mμ was measured. Two ultraviolet-absorbing peaks were observed; the first between fractions 183 and 199, the second between fractions 210 and 232. The former peak was shown by paper chromatography to correspond to P^1P^2-dicytidine-5′ pyrophosphate together with a little cytidine-5′ phosphate, while the latter peak represented CDP-glycerol. CDP-glycerol was obtained free from contamination with non-nucleotide phosphates.

The pooled fractions corresponding to the second peak were neutralised to pH 6·8 with calcium hydroxide solution and evaporated to small bulk under reduced pressure at 30°. Water was removed finally by freeze-drying, and calcium chloride was extracted from the residue by several triturations (6 × 40 c.c.) with ethanol–ether (1 : 1). The calcium salt (0·6 g.), when examined by paper chromatography in *n*-propyl alcohol–ammonia–water (6 : 3 : 1) was shown to contain cytidine-5′ phosphate, glycerol 1 : 2-(hydrogen phosphate), and a trace of inorganic phosphate in addition to CDP-glycerol. As the impurities were not detected in the fraction corresponding to CDP-glycerol obtained directly from the ion-exchange column it was concluded that hydrolysis had occurred during subsequent operations. Spectroscopic measurements indicated about 44% decomposition. The yield of CDP-glycerol before decomposition, calculated as cytidine, from ultraviolet adsorption measurements on the pooled fractions from the ion-exchange resin, was 64%, based on cytidine-5′ phosphate.

A similar synthesis was carried out, starting from barium 2 : 3-*O*-*iso*propylidene-D-glycerol 1-phosphate. Gradient elution was performed in the same apparatus as above, but with 0·02N-hydrochloric acid only in the reservoir flask. The appropriate fractions were neutralised with lithium hydroxide and concentrated to small volume (*ca.* 2 c.c.). The *lithium salt* of CDP-glycerol was obtained by precipitation with acetone (Found: C, 27·3; H, 4·5. $C_{12}H_{19}O_{13}N_3P_2Li_2,2H_2O$ requires C, 27·4; H, 4·4%. Found and calculated P : cytidine = 2·00 : 1). On paper chromatography, followed by inspection under ultraviolet light and development with reagents for glycols or phosphates, the synthetic compound gave a main spot indistinguishable from that given by the natural compound. Cytidine-5′ phosphate (about 7%) and glycerol 1 : 2-(hydrogen phosphate) were also detected. Comparison between synthetic and natural material towards acid, alkali, and snake venom was carried out by methods described earlier.[4]

Paper Chromatography.—Ascending front chromatography on Whatman No. 4 paper was used throughout, the solvents being: A, *n*-propyl alcohol–ammonia (*d* 0·88)–water (6 : 3 : 1), and B, *n*-butyl alcohol–acetic acid–water (4 : 1 : 5) (organic layer).

	R_F in solvents	
	A	B
2 : 3-*O*-*iso*Propylideneglycerol 1-phosphate	0·53	—
Glycerol 1 : 2-(hydrogen phosphate)	0·57	—
CDP-glycerol	0·29	—
Cytidine-5′ phosphate	0·17	0·14
P^1P^2-Dicytidine-5′ pyrophosphate	0·17	0·05

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KING'S COLLEGE, UNIVERSITY OF DURHAM,
NEWCASTLE UPON TYNE.

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630. *The Titration and the Apparent Dissociation Constants of Weak Acids in Mixed Aqueous Solvents.*

By M. K. Hargreaves and P. J. Richardson.

The effect of acetone, ethanol, dioxan, and formaldehyde on the pH-titration curves of weak acids in aqueous solution is recorded. The apparent dissociation constants of alanine in these solvents, determined from the titration curves, are remarkably consistent. The application of corrections for the effect of the non-aqueous component on the electrode system reduces this agreement. It is suggested that amino-acids may buffer the electrode system as between different solvents.

The behaviour of the optical rotatory power of alanine in aqueous acetone and dioxan [1] suggested that loosely bound compounds might be formed in neutral as well as in alkaline [2] solutions. We have examined the effect of dioxan and acetone on the titration of aqueous alanine with sodium hydroxide solution and compared it with the effect on the titration curves of boric acid and phenol. The results of previous work [3] on the titration in aqueous formaldehyde and 20% dioxan are confirmed.

Table 1. *Apparent dissociation constants of weak acids* (0·025N) *in aqueous solvents at* 20°.

Acid	Solvent (%, w/w)	Curve in Fig.	pK_a	pK_a'	pK_a	pK_a'	pK_a/pK_a	pK_b
Alanine	Water	*A*	10·03	10·03	14·00	14·00	1·40	3·97
	8·1% Acetone	*B*	10·03	10·02	14·30	14·28	1·43	4·27
	20·8% Acetone	*C*	10·03	10·00	14·74	14·67	1·47	4·71
	44·2% Acetone	*D*	10·04	9·94	15·60	15·40	1·55	5·56
	70·4% Acetone	*E*	10·19	9·95	16·52	16·04	1·62	6·33
	78·5% Acetone	*F*	10·37	10·04	16·74	16·08	1·61	6·37
	12% Formaldehyde		7·31	7·28	12·06	11·99	1·65	4·75
	25·7% Dioxan	*G*	10·15	10·12	14·66	14·60	1·44	4·51
	50·9% Dioxan	*H*	10·35	10·27	15·32	15·15	1·48	4·97
	75·6% Dioxan	*I*	10·50	10·29	16·72	16·29	1·59	6·22
	20·8% Ethanol		9·94	9·89	14·50	14·41	1·46	4·56
	44·1% Ethanol		10·00	9·88	14·90	14·67	1·49	4·90
	70·0% Ethanol		10·15	9·88	15·88	15·32	1·56	5·63
Glycine	Water		9·88	9·88	14·14	14·14	1·43	4·26
	42·3% Acetone		9·84	9·75	15·74	15·56	1·60	5·90
	67·1% Acetone		9·89	9·68	16·87	16·45	1·71	6·98
	25·7% Dioxan		9·98	9·95	14·36	14·30	1·44	4·38
	50·9% Dioxan		10·16	10·08	14·94	14·77	1·47	4·78
	75·6% Dioxan		10·38	10·17	16·56	16·13	1·60	6·18
Boric acid	Water	*J*	9·22	9·22	14·24	14·24	1·54	5·02
	44·2% Acetone	*K*	11·00	10·90	15·40	15·30	1·40	4·40
	50·9% Dioxan	*L*	11·28	11·20	15·34	15·17	1·36	4·06
	12% Formaldehyde	*M*	8·61	8·58	12·06	11·99	1·40	3·45
Phenol	Water	*N*	9·95	9·95	13·96	13·96	1·40	3·01
	44·2% Acetone	*O*	11·62	11·53	15·24	15·04	1·31	3·62
	50·9% Dioxan	*P*	11·82	11·74	15·24	15·07	1·29	3·42
	12% Formaldehyde	*Q*	9·60	9·57	12·28	12·21	1·28	2·68
Sodium hydrogen carbonate	Water		10·16	10·16	14·12	14·12	1·39	3·96
	44·2% Acetone		11·44	11·34	15·30	15·10	1·34	3·86
	12% Formaldehyde		9·76	9·73	12·38	12·31	1·27	2·52

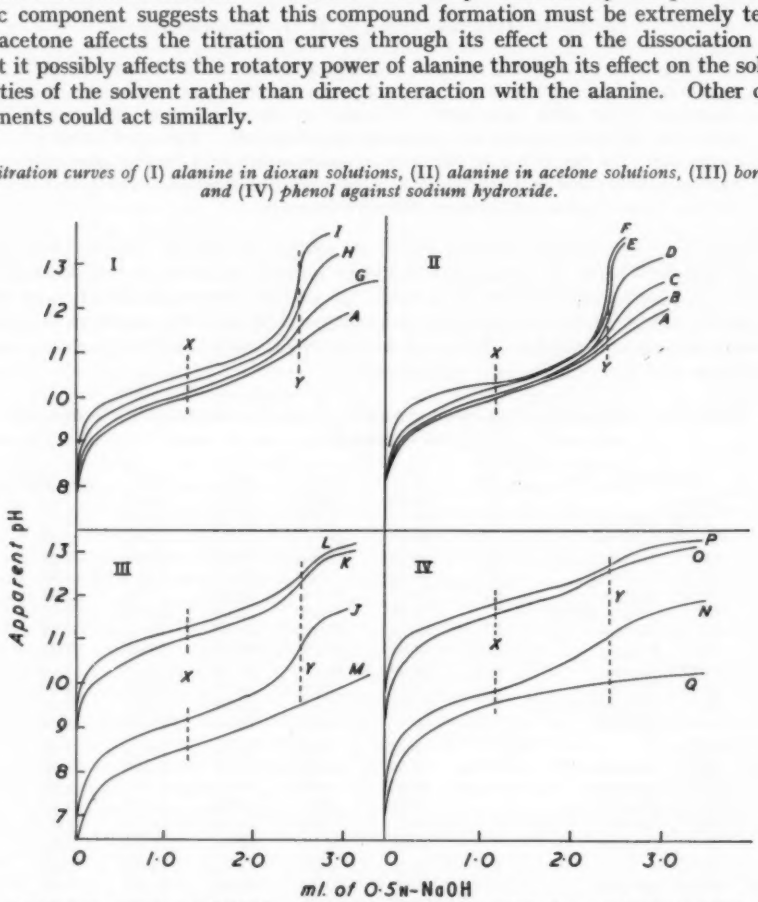
The dissociation constant of alanine is sensibly unaffected by the presence of acetone even in quite high aqueous concentrations. Thus, although acetone facilitates the titration of amino-acids to much the same extent as formaldehyde, it must be for a different reason, since formaldehyde markedly increases the dissociation constant (Table 1). Though

[1] Hargreaves and Richardson, *J.*, 1957, 3823.
[2] Levy, *J. Biol. Chem.*, 1932—33, **99**, 767.
[3] Dunn and Loshakoff, *J. Biol. Chem.*, 1936, **113**, 691; Duggan and Schmidt, *Arch. Biochem.*, 1943, **1**, 453.

XUM

the behaviour of the rotatory power in these solvents is probably best explained in terms of the formation of compounds [1] between the solute and the solvent, the fact that the apparent dissociation constant of alanine is virtually unaltered by the presence of the organic component suggests that this compound formation must be extremely tenuous. Since acetone affects the titration curves through its effect on the dissociation of the solvent it possibly affects the rotatory power of alanine through its effect on the solvating properties of the solvent rather than direct interaction with the alanine. Other organic components could act similarly.

pH-*Titration curves of* (I) *alanine in dioxan solutions,* (II) *alanine in acetone solutions,* (III) *boric acid and* (IV) *phenol against sodium hydroxide.*



For key to curves, see Table 1. X = half-equivalence point, Y = equivalence point.

Form of the Titration Curves.—Potentiometric titration curves of boric acid and of phenol (Fig., III and IV) show that the end-point is not improved on addition of the organic component to the aqueous solvent. Table 1 and the Figure show that a reasonable end-point may be expected when pK_s/pK_a exceeds *ca.* 1·44 for alanine. Solution of the quadratic equation governing this type of equilibrium [4] gives $[H^+] = L^{\frac{1}{2}} - \frac{1}{2}N$. Differentiation of this yields

$$d\,pH/db = -1/(L^{\frac{1}{2}} + \tfrac{1}{2}N) \,.\, [\tfrac{1}{2}L^{\frac{1}{2}}(NS - K_sK_s/b^2) - S]$$

where $L = \frac{1}{4}N^2 + K_sK_s/b$, $N = K_s(1 - a/b) - K_s/b$, $S = (K_sa + K_s)/2b^2$. The roots of L can be positive or negative. K_s is the dissociation constant of the acid, K_s the ionic product of the solvent, and a and b the molar concentrations of acid and base respectively

[4] Glasstone, " An Introduction to Electrochemistry," van Nostrand, New York, 1942, p. 393.

With our values of $a = b = 0{\cdot}025$, $K_a = 10^{-10}$, and $K_s = 10^{-14}$, we obtain approximately, at the end-point

$$\mathrm{d\ pH}/\mathrm{d}b = \pm\sqrt{(K_a/4_aK_s)}$$

This expression provides an alternative method of estimating the sensitivity of the end-point, but it does not take into account deviations from ideality and the actual slope differs from that derived by a factor varying between 1 and 4 so that neither pK_h nor pK_s/pK_a has a definite critical value as between different acids. The slope of the neutralisation curve at the end-point should be inversely proportional to the square-root of the hydrolysis constant, $K_h = K_s/K_a$. Thus a decrease in the ratio $K_a : K_s$ will be accompanied by an increase in the hydrolysis of the salt and also by a reduction in the sensitivity of the end-point.

In the expressions used for K_s the concentration of the solvent is usually taken as constant, but in these mixed solvents it is desirable to allow for the varying proportions of the water. A full allowance for the solvating properties of water ($HOH + HOH \rightleftharpoons H_3O^+ + OH^-$) leads to the expression $K_s' = K_s/N^2$ where N is the mole-fraction of water in the solvent, whereas only a single exponent for N is required if the organic component takes part in the solvation preferentially. The use of the mole fraction instead of molar concentration follows Gutbezahl and Grunwald,[5] pK_s' thus having the same numerical value and the same dimensions as pK_w in pure water.

Similarly the equilibrium constant of the reaction $HA + HOH \rightleftharpoons H_3O^+ + A^-$ is given by $K_a' = K_a/N$. Table 1 shows that pK_a' varies rather less than pK_s, as expected, but it seems likely that the mole-fraction term over-corrects the expression since solvolysis may also occur with the organic component.

To the nearest unit in the second decimal place of pH units the Henderson equation $pK = \mathrm{pH} + \log[HA]/[A^-]$ can be substituted for the equation governing this type of equilibrium so that pK can be determined as the pH at half-neutralisation. pK_s can similarly be determined from the pH at the neutral point from $\mathrm{pH} = \frac{1}{2}pK_a + \frac{1}{2}pK_s + \frac{1}{2}\log c$, where c is the concentration of the salt produced.

Variation of the Apparent Dissociation Constant with Solvent.—The effectiveness of acetone and dioxan in improving the end-point in the titration of amino-acids is due to their effect on K_s rather than on the dissociation constant of the amino-acid. With boric acid and phenol the acid dissociation constants are moved nearer to the dissociation constant of the solvent by the organic component so that the end-point is worse. Table 1 shows how pK_a and pK_s are affected. It is noteworthy that formaldehyde affects the pK_a for alanine much more than does acetone or dioxan; its effect is also opposite in sign to that of the other organic components. This seems to be attributable to compound formation.

The contrasting behaviour of the amino-acids and that of the other acids studied may be related to the effect of the dielectric constant of the solution on the dissociation of acids of ammonium-ion type and of acids where positive and negative charges are separated in the process. The effect of dielectric constant may in turn be linked with the state of solvation of the respective ions or molecules. The hydrogen ion, being common to both types of acid, cannot be involved in the difference in their behaviour. The small change observed in the apparent pK_a of the amino-acids as the aqueous solution is diluted with the organic component suggests that the difference between the solvation energies in water and in the organic liquid of the acid must be similar to that of its dissociated parts.

Harned and Birdsall's [6] results for glycine (as calculated by Robinson and Stokes [7]) do not show this constancy; their dissociation constants, which were extrapolated to zero ionic strength, decrease more markedly with the proportion of dioxan. On the other

[5] Gutbezahl and Grunwald, *J. Amer. Chem. Soc.*, 1953, **75**, 565.
[6] Harned and Birdsall, *ibid.*, 1943, **65**, 1117.
[7] Robinson and Stokes, "Electrolyte Solutions," Butterworths, London, 1955, p. 504.

XUM

hand Lonning and Treadwell's [8] results for glycine in acetone are more in agreement with this work.

With aliphatic carboxylic acids pK_h varies much less in aqueous dioxan than does pK_h of alanine (Table 2; calculated from Harned and Owen's results [9]). pK_a increases with pK_s as the organic component is added, and pK_s/pK_a is thus decreased and the end-

TABLE 2. pK_h *of carboxylic acids in aqueous dioxan solution.*

Dioxan (%, w/w)	Formic acid	Acetic acid	Propionic acid
0	10·41	9·41	9·24
20	10·61	9·50	9·32
45	10·83	9·60	9·36
70	11·02	9·70	9·40

point rendered less satisfactory. The fact that carboxylic acids dissociate less readily in aqueous dioxan than in water [9] may mean that the ions are less extensively solvated than in water. The molecular and ionic species of the amino-acids, on the other hand, appear to be solvated to about the same relative extent in all solvents studied. At all concentrations used here there was always sufficient water present to provide a sheath around the acid species.

Table 1 shows that the apparent dissociation constant of alanine and of glycine in aqueous acetone varies very little up to a concentration of 70% of acetone, agreeing very well with those obtained in pure water. Alcohol–water mixtures show a similar constancy and dioxan–water mixtures produce a slightly greater variation.

Correction for the Effect of the Solvent on the Liquid Junction.—The theoretical difficulties of treating such systems absolutely made us attempt to determine an empirical correction to enable these results to be compared with those obtained in pure water. Such a correction was suggested by van Uitert and Haas,[10] and in a different form by Gutbezahl and Grunwald: [5]

$$pH_A = pH^s_A + C,\ pH_B = pH^s_B + C$$

where C is a term correcting for the effect of the organic component in the solvent. Then $pH_A = pH^s_A + pH_B - pH^s_B$. The subscripts A and B refer to the test solution and to a standard solution of hydrochloric acid respectively, and the superscript denotes a mixed aqueous solvent. The values are given in Table 3. This correction is only strictly valid

TABLE 3. *Empirical electrode corrections for mixed aqueous solvents.*

(%, w/w) *	A †	$M_A - M^s_A$	Sum ‡	(%, w/w) *	A †	$M_A - M^s_A$	Sum ‡	(%, w/w) *	A †	$M_A - M^s_A$	Sum ‡
	Acetone				Ethanol				Dioxan		
10·2	0·996	0·06	0·06	9·9	0·977	0·02	0·02	12·9	0·998	0·04	0·05
20·8	0·993	0·10	0·10	20·8	0·958	−0·01	0·00	25·7	0·996	0·03	0·04
32·2	0·989	0·10	0·11	32·1	0·949	−0·05	−0·04	38·3	0·989	0·04	0·05
44·2	0·986	0·14	0·15	39·2	0·942	−0·11	−0·09	50·9	0·968	0·13	0·16
56·7	—	0·24	—	44·1	0·932	−0·18	−0·16	63·1	0·904	0·27	0·31
70·4	—	0·49	—	56·8	0·924	−0·25	−0·23	75·6	0·815	0·74	0·87
				70·0	0·906	−0·33	−0·29				

* Of component shown in centre heading.
† A = estimated mean activities (from references 11 and 12) used to calculate column 4.
‡ Sum $= M_A - M^s_A + \log (a_A/a^s_A)$.

if the protonic activities are identical in the test and in the standard solution, but using estimated values for the activities of the hydrogen ion [11,12] we can derive a correction

[8] Lonning and Treadwell, *Helv. Chim. Acta*, 1945, **28**, 1037.
[9] Harned and Owen, "Physical Chemistry of Electrolytic Solutions," Reinhold, New York, 1950, p. 581.
[10] van Uitert and Haas, *J. Amer. Chem. Soc.*, 1953, **75**, 451.
[11] Feakins and French, *J.*, 1956, 3168.
[12] Ref. 9, pp. 548, 550.

which involves only the junction potential by standardising the meter with two buffer solutions so that the meter readings $M_{S,1} = -\log a_{S,1}$ and $M_{S,2} = -\log a_{S,2}$. But the meter measures e.m.f., E, which is given by:

$$E_{S,1} = -\phi \log a_{S,1} + E^1$$
$$E_{S,2} = -\phi \log a_{S,2} + E^1$$

Similarly for the test solutions:

$$E_A = -\phi \log a_A + E^1 \; ; \; E_B = -\phi \log a_B + E^1$$

and in mixed solvents

$$E^s_A = -\phi \log a^s_A + E^{1s} \; ; \; E^s_B = -\phi \log a^s_B + E^{1s}$$

thus $\log a^s_B$ can be evaluated * if the values for solution A are known and on the assumption that the liquid junctions are similar for A and B.

Then, since $M_B = -\log a_B$:

$$-\log a^s_B = M^s_B + (M_A - M^s_A) + \log (a_A/a^s_A)$$

which is reasonable where a saturated potassium chloride bridge is employed. An uncertainty is, however, introduced since the anions are different in the test solution and in the check solution. Since the anions due to the salt bridge are in such excess, this objection is not likely to be serious at the present level of accuracy

This type or correction is found to be rather large (Table 1) and would destroy the constancy of the apparent pK_a for alanine. The values given in Table 3 are readings of e.m.f. given on a scale with fixed points determined with aqueous buffer solutions (solutions of constant hydrogen-ion activity and e.m.f., and thus of constant available energy). The constancy of pK_a in Table 1 thus implies a constancy in pH and thus in e.m.f. and available energy.

When the pH scale is calibrated in terms of buffer solutions the meter readings are related as follows for two solutions X and Y:

$$M_X - M_S = \log a_S - \log a_X + (E^1_X - E^1_S)/\phi$$
$$M_Y - M_S = \log a_S - \log a_Y + (E^1_Y - E^1_S)/\phi$$

When $M_X = M_Y$, as with water and 20% acetone solutions of alanine,

then $$\log a_Y - \log a_X = (E^1_Y - E^1_X)/\phi$$

Thus for a solution of the acid in two different solvent mixtures the change in the liquid-junction potential is balanced by a change in the activity of the hydrogen ion.

The fact that the observed e.m.f.s of cells containing alanine at half-neutralisation in various acetone–water and ethanol–water mixtures do not vary suggests that a kind of buffering action may occur since with the strong acid, hydrochloric, there is a definite difference in the e.m.f.s observed in the two solvents. This buffering effect is not observed with the weak acids since their dissociation constants vary too greatly with the solvent. It is impossible to compare directly the effect of the components of the mixed solvents on the e.m.f. of a strong acid in the region of pH greater than 7; comparison with solutions of strong alkali are not direct since the electrode is sensitive to hydrogen ions only and above pH 7 operates by virtue of the ionic product, which is not constant as between different solvent mixtures.

* $\phi M_A = E_A - E^1$; $\phi M^s_A = E^s_A - E^1$; $E^s_A = -\phi \log a^s_A + E^{1s}$
$\phi M_B = E_B - E^1$; $\phi M^s_B = E^s_B - E^1$, $E^s_B = -\phi \log a^s_B + E^{1s}$
$M_A - M^s_A = \log (a^s_A/a_A) + (E^1 - E^{1s})/\phi$; $\phi = (E_{s,1} - E_{s,2})/(M_{s,1} - M_{s,2})$
E^1 and E^{1s} include the standard cell potentials and the respective liquid junction potentials.

XUM

The dissociation of amino-acids has been compared with that of the ammonium ion.[13] It seemed interesting to see how far the results obtained for amino-acids are paralleled by the dissociation of ammonium chloride. These results are given in Table 4; those for

TABLE 4. *Apparent* pK_a *of the ammonium ion at 20° in mixed solvents.*

Solvent	pK_a	pK_a	Solvent	pK_a	pK_a
Water	9·41	14·04	44·2% Acetone	9·17	15·76
44·1% Ethanol	9·17	14·90	50·9% Dioxan	9·17	14·86
14·6% Formaldehyde	3·68	13·88			

Solutions.—25 ml. of 0·0509N-ammonium chloride solution diluted with 25 ml. of water, acetone, dioxan, or 25·3% formaldehyde solution.

formaldehyde solution cannot be exact because formaldehyde reacts slowly with ammonium chloride giving substituted ammonias.[14] It is noteworthy that there is a definite decrease in the apparent pK_a on the introduction of 50% of organic component into the solvent. Thus, the liquid-junction potential being neglected, the activity of the hydrogen ion is apparently greater in the mixed solvents than in water. This agrees with the results obtained by Gutbezahl and Grunwald[15] for anilinium and ammonium salts in ethanol–water mixtures but contradicts the findings for aliphatic and hydroxy-acids.[16] Braude and Stern[17] have discussed this type of effect in terms of the quasi-crystalline structure of aqueous solutions, suggesting that in a solution containing some organic diluent the crystalline structure will be less evident and the freedom of the ions and thus their activities greater. In this case an alternative explanation may lie in the liquid-junction potential.

EXPERIMENTAL

A Cambridge portable pH meter calibrated to 0·02 pH unit and read to 0·01 unit was used. It was standardised with electrometrically checked buffer solutions (British Drug Houses Ltd.) at pH 3·96 and 9·21. The cell was a Cambridge wide-range glass electrode in conjunction with the standard calomel electrode.

Procedure.—In each titration 50 ml. of the acid (0·025N) in a deep 100 ml. beaker were titrated with 0·5N-sodium hydroxide solution, a micro-burette fitted with a fine hypodermic needle as the jet being used. The beaker was immersed in a copper thermostat tank (at 20° ± 0·1°) which acted as an electrical screen. A steady stream of nitrogen from a cylinder was passed through all solutions. For alkaline solutions the mouth of the beaker was packed with cotton wool (under these conditions a solution of sodium hydroxide maintained a constant pH of 9·48 for ½ hr., but without the cotton wool the pH fell to 7·93 in ½ hr.

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QUEEN ELIZABETH COLLEGE, LONDON, W.8. [*Received, February 26th,* 1958.]

[13] Ref. 4, p. 418.
[14] Werner, *J.*, 1917, **111**, 844.
[15] Gutbezahl and Grunwald, *J. Amer. Chem. Soc.*, 1953, **75**, 559.
[16] Grunwald and Berkowitz, *ibid.*, 1951, **73**, 4939.
[17] Braude and Stern, *J.*, 1948, 1976.

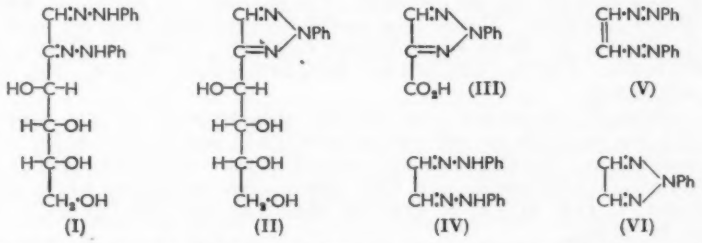
631. *The Scope and Mechanism of Carbohydrate Osotriazole Formation. Part II.* The Action of Oxidising Agents on Osazones and Osotriazoles.*

By H. El Khadem and Zaki M. El-Shafei.

Conversion of glucose arylosazones into osotriazoles by copper or iron salts, or by bromine water, is due to oxidation. Stronger oxidising agents yield 2-aryl-1 : 2 : 3-triazole-4-carboxylic acids.

Carbohydrate phenylosazones are converted into phenylosotriazoles and aniline when refluxed in aqueous copper sulphate.[1] Teuber and Jellinek [2] recently effected a similar change by nitrosodisulphonate. In the present work various inorganic salts were refluxed with aqueous suspensions of glucose phenylosazone (I): cupric chloride, nitrate, and acetate, ferric chloride, ferric sulphate, and potassium ferricyanide readily yielded glucose phenylosotriazole (II). The corresponding salts in lower states of valency and salts with no oxidising character were ineffective.

Other oxidising agents were also used; bromine water with glucose phenylosazone (I) in the cold yielded glucose *p*-bromophenylosotriazole, directly obtained also from glucose phenylosotriazole and bromine water. The fact that *p*-bromophenylosotriazoles are less soluble than the corresponding phenyl derivatives, together with the simplicity and good yields obtained, render this reaction of value for the identification of osazones and osotriazoles.



Bromine water seems to have a dual function; that of converting the osazones into the osotriazoles and of brominating them in the *para*-position. Aryl osazones in which the *para*-position was occupied, as in glucose *p*-tolylosazone and *p*-bromophenylosazone, were merely converted into the corresponding tolyl- and *p*-bromophenyl-osotriazole.

On treatment with strong oxidising agents such as neutral potassium permanganate, potassium dichromate, or 20% nitric acid glucose phenylosazone yielded in small amounts 2-phenyl-1 : 2 : 3-triazole-4-carboxylic acid (III) and benzoic acid; the latter was probably formed by degradation of the osazone before the triazole was formed, since glucose phenylosotriazole on similar treatment yielded 2-phenyl-1 : 2 : 3-triazole-4-carboxylic acid nearly quantitatively.

Potassium permanganate readily converted glucose *p*-tolylosotriazole into 2-*p*-carboxyphenyl-1 : 2 : 3-triazole-4-carboxylic acid, and glucose *p*-bromophenylosotriazole into 2-*p*-bromophenyl-1 : 2 : 3-triazole-4-carboxylic acid. The latter acid was also obtained by treating 2-phenyl-1 : 2 : 3-triazole-4-carboxylic acid with bromine water.

From the above it is clear that closure of the triazole ring is achieved through oxidation of the sugar osazone. In the case of simple osazones such as glyoxal phenylosazone (IV) it was shown by von Pechmann [3] that oxidation with potassium dichromate yielded a

* Part I, *J.*, 1953, 3452.

[1] Hann and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 735; 1945, **67**, 939; 1946, **68**, 1766.
[2] Teuber and Jellinek, *Chem. Ber.*, 1952, **85**, 95.
[3] von Pechmann, *Ber.*, 1888, **21**, 2751.

XUM

stable red compound which was given a cyclic tetrazine structure, but later [4] ascribed structure (V). This was converted by boiling dilute acid or alkali into 2-phenyl-1 : 2 : 3-triazole (VI) and aniline. In the present work, it was found that refluxing glyoxal phenylosazone (IV) with aqueous cupric sulphate gave 2-phenyl-1 : 2 : 3-triazole (VI) and aniline; but at room temperature 1 : 2-bisphenylazoethylene (V) was obtained. This suggests that, when refluxed with cupric sulphate, the osazone is first oxidised to the intermediate (V), then decomposed to the triazole and aniline.

The ultraviolet absorption spectra of the triazoles are characterised by a single peak between 262 and 282 mμ (see Table).

	$\lambda_{max.}$ (mμ)	Log ε
Glyoxal phenylosotriazole	262	4·14
Glucose phenylosotriazole	268	4·33
Glucose *p*-bromophenylosotriazole	274	4·46
Glucose *p*-tolylosotriazole	268—272	4·39
2-Phenyltriazole-4-carboxylic acid	270	4·35
2-*p*-Carboxyphenyltriazole-4-carboxylic acid	282	4·53
2-*p*-Bromophenyltriazole-4-carboxylic acid	280	4·45

Experimental

Absorption spectra were determined for EtOH solutions with a Unicam S.P. 500 spectrophotometer. Microanalyses were by A. Bernhardt, Mülheim, W. Germany.

Glucose Phenylosotriazole (II) *from the Phenylosazone* (I) *by means of Cupric and Ferric Salts.*—Suspensions of glucose phenylosazone (2 g.) were refluxed with the salt until dissolved. The whole was filtered while hot and left overnight. The products were filtered off, washed with water and ethanol, and dried. Glucose phenylosotriazole crystallised from hot water and was identified by a mixed m. p. Yields were as follows: $CuSO_4$ 59% in 4 hr.; $CuCl_2$ 62% in 0·5 hr.; $Cu(NO_3)_2$ 55% in 3 hr.; $Cu(OAc)_2$ 53% in 2 hr.; $FeCl_3$ 29% in 1 hr.; $Fe_2(SO_4)_3$ 18% in 0·5 hr.; $K_3Fe(CN)_6$ 66% in 3 hr.

Glucose p-*Bromophenylosotriazole.*—(*a*) Glucose phenylosazone (2 g.), suspended in water (100 ml.), was treated in the cold with bromine (1 ml.), and the mixture kept overnight. The brown mass obtained was filtered off and washed with water and ethanol (yield 1·5 g.). It recrystallised from ethanol in needles, m. p. 225°, alone or mixed with glucose *p*-bromophenylosotriazole [5] (Found: C, 41·5; H, 4·2; N, 12·0; Br, 23·5. Calc. for $C_{12}H_{14}O_4N_3Br$: C, 41·9; H, 4·1; N, 12·2; Br, 23·3%).

(*b*) Glucose phenylosotriazole (2 g.), similarly treated, gave the same product, m. p. and mixed m. p. 225° (Found: C, 41·9; H, 4·1; N, 12·0; Br, 23·3%).

(*c*) Glucose *p*-bromophenylosazone (1 g.) in water (50 ml.) was treated with bromine (1 ml.) as above, giving glucose *p*-bromophenylosotriazole (0·4 g.), m. p. and mixed m. p. 225°.

Galactose p-*Bromophenylosotriazole.*—Galactose phenylosotriazole (0·5 g.) in water (50 ml.) was treated with bromine (0·5 ml.) as above, giving galactose *p*-bromophenylosotriazole (0·4 g.), m. p. 159°, not depressed by admixture with an authentic specimen [5] (Found: C, 41·6; H, 4·1; N, 12·3; Br, 23·4%).

Glucose p-*tolylosotriazole*, obtained (0·8 g.) from glucose *p*-tolylosazone (1 g.) in water (50 ml.) with bromine (1 ml.) as above and crystallised from water–ethanol, had m. p. 204° alone or mixed with authentic osotriazole [6] (Found: C, 55·8; H, 6·3; N, 15·1. Calc. for $C_{13}H_{17}O_4N_3$: C, 55·9; H, 6·1; N, 15·1%).

2-*Phenyl*-1 : 2 : 3-*triazole*-4-*carboxylic Acid* (III).—(*a*) A boiling solution of glucose phenylosotriazole (2 g.) in water (250 ml.) was treated with potassium permanganate (7 g.) in small portions. The hot mixture was filtered, treated with sodium hydrogen sulphite, and acidified with concentrated hydrochloric acid. The crystals (1·2 g.) that separated recrystallised from water–ethanol in needles, m. p. 191°, alone or mixed with 2-phenyl-1 : 2 : 3-triazole-4-carboxylic acid [7] (Found: C, 57·1; H, 3·7; N, 22·0. Calc. for $C_9H_7O_2N_3$: C, 57·1; H, 3·7; N, 22·2%).

[4] Stollé, *Ber.*, 1926, **59**, 1742.
[5] Hardegger, El Khadem, and Schreier, *Helv. Chim. Acta*, 1951, **34**, 253.
[6] Hardegger and El Khadem, *ibid.*, 1947, **30**, 1478.
[7] Hardegger and Schreier, *ibid.*, 1952, **35**, 232.

(*b*) A boiling suspension of glucose phenylosazone (10 g.) in water (500 ml.) was treated with potassium permanganate (60 g.) during 1 hr. The hot mixture was filtered, treated with sodium hydrogen sulphite, and acidified, and extracted with ether. The extract on evaporation gave a residue (1 g.) which sublimed at 10 mm. At 80°, benzoic acid sublimed (m. p. and mixed m. p. 121°). A fraction which sublimed at 150°, in colourless needles, m. p. 191°, was 2-phenyl-1 : 2 : 3-triazole-4-carboxylic acid.

(*c*) A suspension of glucose phenylosazone (10 g.) in water (250 ml.) was either heated for 1 hr. with potassium dichromate (60 g.) and 25 ml. of acetic acid or treated in the cold for 12 hr. with 70% nitric acid (100 ml.), then extracted with ether and treated as above, giving benzoic acid and 2-phenyl-1 : 2 : 3-triazole-4-carboxylic acid. The yield was however poor.

2-p-*Carboxyphenyl*-1 : 2 : 3-*triazole*-4-*carboxylic Acid*.—To a boiling solution of glucose *p*-tolylosotriazole (0·5 g.) in water (150 ml.), potassium permanganate (3 g.) was added gradually. The hot mixture was filtered, treated with sodium hydrogen sulphite, and acidified, giving crystals (0·2 g.) which recrystallised from ethanol in colourless needles, m. p. 344° (decomp.). 2-p-*Carboxyphenyl*-1 : 2 : 3-*triazole*-4-*carboxylic acid* is moderately soluble in hot ethanol and methanol and insoluble in water (Found: C, 51·3; H, 3·0; N, 17·9. $C_{10}H_7O_4N_3$ requires C, 51·5; H, 3·0; N, 18·0%).

2-p-*Bromophenyl*-1 : 2 : 3-*triazole*-4-*carboxylic Acid*.—(*a*) A boiling suspension of glucose *p*-bromophenylosotriazole (2·3 g.) in water (150 ml.) was treated with solid potassium permanganate (6 g.). The hot mixture was filtered, treated with sodium hydrogen sulphite, and acidified. The crystals (1 g.) recrystallised from water–ethanol in needles, m. p. 236°. 2-p-*Bromophenyl*-1 : 2 : 3-*triazole*-4-*carboxylic acid* is soluble in ethanol and methanol and insoluble in acetone and water (Found: C, 40·6; H, 2·3; N, 15·6; Br, 29·9. $C_9H_6O_2N_3Br$ requires C, 40·3; H, 2·2; N, 15·7; Br, 29·9%).

(*b*) A cold suspension of 2-phenyl-1 : 2 : 3-triazole-4-carboxylic acid (0·6 g.) in water (50 ml.) was treated with bromine (1 ml.) and left overnight. The almost colourless solid obtained was filtered off, washed with water (0·5 g.), and recrystallised from water–ethanol in colourless needles, m. p. 236° alone or mixed with 2-*p*-bromophenyl-1 : 2 : 3-triazole-4-carboxylic acid (Found: C, 40·5; H, 2·4; N, 15·5%).

2-*Phenyl*-1 : 2 : 3-*triazole* (VI) *from Glyoxal Phenylosazone* (IV) *and Copper Sulphate*.—Glyoxal phenylosazone (7 g.) was suspended in a solution of copper sulphate (7 g.) in water (350 ml.) and refluxed for 1·5 hr. The solution was then steam-distilled and the distillate (200 ml.) extracted with ether. The ethereal layer was washed with dilute hydrochloric acid to remove aniline, and dried (Na_2SO_4). The oily residual *triazole* after removal of the ether was purified by repeated distillation (80°/12 mm.) (Found: C, 66·5; H, 4·9; N, 28·7. $C_8H_7N_3$ requires C, 66·2; H, 4·8; N, 29·0%).

1 : 2-*Bisphenylazoethylene* (V) *from Glyoxal Phenylosazone* (IV) *and Copper Sulphate*.—Glyoxal phenylosazone (0·6 g.) was suspended in a solution of copper sulphate (0·6 g.) in water (100 ml.) and the mixture kept at room temperature for 30 days. The osazone gradually became reddish-brown (after one week). The suspension was filtered and the product recrystallised from ethanol in dark red plates, m. p. 150°, not depressed on admixture with 1 : 2-bisphenylazoethylene prepared by the action of potassium dichromate on glyoxal phenylosazone [3] (Found: C, 70·9; H, 4·8; N, 23·5. Calc. for $C_{14}H_{12}N_4$: C, 71·2; H, 5·1; N, 23·7%).

Thanks are offered to Professor G. Soliman for valuable discussions.

FACULTY OF SCIENCE, ALEXANDRIA UNIVERSITY,
ALEXANDRIA, EGYPT.

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XUM

632. *Complex Formation between Ferric Ion and Glycine.*

By D. D. Perrin.

In acid solution ferric ion and glycine form a stable 1 : 1 complex. A consistent value of 10^{10} for the stability constant of the complex was obtained from measurements of oxidation–reduction potential and spectrophotometry. The ferric–glycine complex is more stable than the corresponding cupric complex.

Although ferrous ion, like most bivalent cations, forms chelate compounds with α-amino-acids [1,2,3] little evidence of complex formation between ferric ion and amino-acids has been reported. An unstable violet complex is formed by ferric ion in cysteine solutions; [4] over the range pH 10—11, the complexes $FeOH(RS)_2^{2-}$ and $Fe(RS)_3^{3-}$, where RS is the cysteine di-anion, are present.[5] It is likely that these complexes involve linkages through the sulphur atoms. For the remaining amino-acids the most positive finding seems to be that with phenol as solvent ferric ion is moved along a paper chromatogram by histidine and to a much smaller extent by a number of other amino-acids.[6] On the other hand, measurement of pH changes during acid–base titration of amino-acid solutions containing ferric ion did not suggest any interaction, except possibly for aspartic acid.[2,3] However, this procedure was somewhat uncertain because under the necessary experimental conditions hydrolysis of ferric ion was considerable and led, at an early stage in the titration, to the separation of a basic sulphate. Hydrated ferric ion is appreciably hydrolysed even in solutions of pH 2, hydrolysis increasing very sharply as the solution is made less acid, and the solubility of ferric hydroxide is so low (solubility product less than 10^{-35} at 20° c [7]) that unless strongly complex-forming reagents are present, precipitation occurs from neutral or weakly acid solutions even for micromolar concentrations of ferric ion.

Formation of metal complexes with amino-acids should involve a large favourable entropy change because of the accompanying reduction of ionic charge.[8] As this effect is greater the smaller the ion and the higher its charge,[9] ferric ion should form more stable complexes with anions than does ferrous ion. Differences in electronegativity point to the same conclusion. The behaviour of ferric ion with glycine, the simplest α-amino-acid, has therefore been re-examined by measurements of oxidation–reduction potentials and spectrophotometry.

Experimental

All reagents were of analytical grade. Ferric hydroxide, prepared by precipitation from hot ferric sulphate solution with ammonia, was washed thoroughly at the centrifuge and dissolved in excess of perchloric acid. The ferric ion concentration was checked by reduction with zinc amalgam and titration with standard potassium dichromate. Perchloric acid in the ferric perchlorate solution was determined by back-titration of excess of hot sodium hydroxide solution, allowance being made for the complete hydrolysis of the ferric perchlorate. Ferrous perchlorate, prepared by double decomposition between barium perchlorate and ferrous sulphate, was standardised against potassium dichromate.

To minimise formation of ferric hydroxyl complexes and colloidal ferric hydroxide all measurements were made at pH 0·5—4·6. High concentrations of glycine were necessary because of the very small fraction present as anion under these conditions. As glycine acts as a buffer over this pH range, high concentrations of acid were also required. Ferric ion forms

[1] Flood and Lorås, *Tidsskr. Kjemi Bergvesen Met.*, 1945, **5**, 83; Maley and Mellor, *Nature*, 1950, **165**, 453.
[2] Albert, *Biochem. J.*, 1950, **47**, 531.
[3] *Idem*, *ibid.*, 1952, **50**, 690.
[4] Cannan and Richardson, *ibid.*, 1929, **23**, 1242.
[5] Tanaka, Kolthoff, and Stricks, *J. Amer. Chem. Soc.*, 1955, **77**, 1996, 2004.
[6] Gabrio and Tishkoff, *Science*, 1950, **112**, 358.
[7] Evans and Pryor, *J.*, 1949, S157.
[8] Williams, *J.*, 1952, 3770.
[9] Powell and Latimer, *J. Chem. Phys.*, 1951, **19**, 1139.

complexes with most inorganic anions, but a complex is not formed between ferric ion and perchlorate ion for perchlorate concentrations [10] up to 3M. Under the present experimental conditions about 4% of the ferric ion not present in complexes would exist [11] as ferric perchlorate ion-pairs. This would not significantly affect the results. Perchloric acid was used throughout, with the addition of sodium perchlorate to maintain a constant ionic strength of 1·0. In computing ionic strength the zwitterion form of glycine was considered as a neutral molecule.[12]

Oxidation–Reduction Potentials.—The potentiometer was a Tinsley type 4046B, easily readable to 0·1 mv, and was used with a Pye " Scalamp " galvanometer. Two bright platinum electrodes in the solution were connected to a large saturated calomel electrode by an ammonium nitrate (1·60M)–sodium nitrate (0·20M)–agar bridge. (Potassium chloride or nitrate bridges

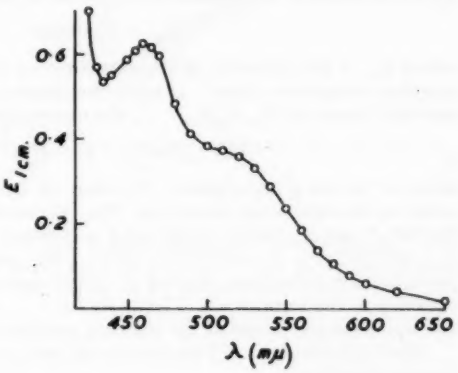

FIG. 1. *Absorption spectrum of ferric–glycine complex.*
Ferric ion, 0·0166M; glycine, 1·20M; pH 2·23.

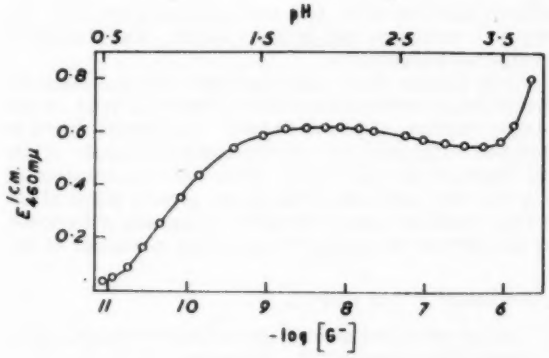

FIG. 2. *Variation of optical density with glycine anion concentration.*
Ferric ion, 0·0166M.

were unsatisfactory owing to precipitation of potassium perchlorate at the liquid junction.) Adjusted to pH 7, this salt mixture gave equal cation and anion conductances but did not precipitate ammonium perchlorate. All pH measurements were made on a Cambridge bench model pH meter with a glass electrode–saturated calomel electrode combination, separated by an ammonium nitrate–sodium nitrate bridge. The pH standard taken was 0·050M-potassium hydrogen phthalate, pH 4·00. Commercial nitrogen, passed through Fieser's solution, was used to stir the solution in the electrode vessel and to maintain an inert atmosphere. All potentiometric measurements were made at 20° ± 0·1°.

From the ionisation constants of glycine and the stability constants of the ferrous–glycine complexes [13] it can be calculated that, even at a glycine concentration of 1M, ferrous complex

[10] Rabinowitch and Stockmayer, *J. Amer. Chem. Soc.*, 1942, **64**, 335.
[11] Sutton, *Nature*, 1952, **169**, 71.
[12] King, *J. Amer. Chem. Soc.*, 1945, **67**, 2178; Scatchard and Kirkwood, *Phys. Z.*, 1932, **33**, 297.
[13] Albert, *Biochem. J.*, 1953, **54**, 646.

formation is negligible in solutions more acid than pH 4. Under such conditions the oxidation–reduction potentials of solutions of known ferrous-ion concentration can be used to study complex formation involving ferric ion.[14] At 20° the potential of the cell

$$\text{Pt} \left| \begin{matrix} Fe^{3+} & ClO_4^- \\ Fe^{2+} & H^+ \\ \multicolumn{2}{c}{\text{glycine}} \end{matrix} \right| \quad \text{sat. KCl} \quad \Big| \ \text{calomel}$$

is $E = E_0 + 0{\cdot}0581 \log (a_{Fe^{3+}}/a_{Fe^{2+}}) + E_j$, where E_0 is a constant and E_j is the liquid-junction potential. If the approximations are made that at constant ionic strength the liquid-junction potential and the activity coefficients of ferric and ferrous ions do not change appreciably when glycine is added to the solution or the pH of the solution is altered it follows that

$$(E_0' - E)/0{\cdot}0581 = \log ([Fe^{3+}]_0/[Fe^{3+}]) \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where E_0' is the potential of the experimental ferric–ferrous ratio under conditions where no complex formation occurs. If ferric ion forms 1 : 1, 1 : 2, and higher complexes with overall stability constants K_1, K_1K_2, . . ., the mass-action equation can be written

$$[Fe^{3+}]_0/[Fe^{3+}] = 1 + K_1[G^-] + K_1K_2[G^-]^2 + \ldots \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where G^- is the glycine anion. To allow for hydrolysis of ferric ion additional terms must be added to the right-hand side of eqn. (2). Estimates of contributions due to the species $FeOH^{2+}$, $Fe(OH)_2^+$, and $Fe_2(OH)_2^{4+}$ at 20° and $I = 1$, based on published data,[15,16,17] are $1 \times 10^{-3}/[H^+] + 4 \times 10^{-7}/[H^+]^2 + 2 \times 10^{-3}[Fe^{3+}]/[H^+]^2$. By plotting $[Fe^{3+}]$, obtained from eqn. (1) and corrected for hydrolysis, against $[G^-]$ and endeavouring to fit the experimental data by an equation of the form, $y = 1 + ax + bx^2 + \ldots$, evidence of complex formation can be sought and approximate values of the stability constants obtained.

Spectrophotometry.—All measurements were made at 25° ± 1° on a Hilger Uvispek H700/305 spectrophotometer.

Concentrated glycine solutions buffered with perchloric acid and containing ferric ion are amber-coloured, the intensity increasing to a maximum with increase of pH. The absorption spectrum, shown in Fig. 1, is not due to the ion $FeOH^{2+}$.[10]

If the assumption is made that at low glycine anion concentrations only one complex, $FeG_n^{(3-n)+}$ is formed, the variation of optical density with change of pH enables the glycine : ferric ion ratio of the complex, and the stability constant, to be determined. The results shown in Fig. 2 were obtained by progressive addition of 5M-perchloric acid to a solution initially of pH 3·85 and 2M in glycine. The optical densities are for a total ferric ion concentration of $1{\cdot}66 \times 10^{-2}$M. Because the complex is the only light-absorbing species present below about pH 2, the flat portion of the curve in Fig. 2 indicates almost complete conversion of ferric ion to ferric–glycine complex. Over this flat portion the molecular extinction coefficient of the complex is given by:

$$E_{1\,\text{cm.}} = \varepsilon[FeG_n^{(3-n)+}] \simeq \varepsilon[Fe^{3+}]_0$$

Hence values of $[FeG_n^{(3-n)+}]$ and $[Fe^{3+}]$ can be calculated at lower glycine anion concentrations. But, at constant ionic strength, $K_n = [FeG_n^{(3-n)+}]/[Fe^{3+}][G^-]^n$. Therefore,

$$\log ([FeG_n^{(3-n)+}]/[Fe^{3+}]) = \log K_n + n \log [G^-] \quad . \quad . \quad . \quad . \quad (3)$$

The plot of the left-hand side of eqn. (3) against $\log [G^-]$ gives n and $\log K_n$.

Results

Ionisation constants for glycine at 20° in a solution of unit ionic strength were determined by potentiometric titration to be 2·43 and 9·76. By using the small temperature corrections given by Owen,[18] values at 25° were obtained as 2·41 and 9·73.

[14] Ågren, *Acta Chem. Scand.*, 1954, **8**, 266; Perrin, *J. Amer. Chem. Soc.*, in the press.
[15] Siddall and Vosburgh, *J. Amer. Chem. Soc.*, 1951, **73**, 4270.
[16] Hedström, *Arkiv Kemi*, 1953, **5**, 457; **6**, 1.
[17] Mulay and Selwood, *J. Amer. Chem. Soc.*, 1955, **77**, 2693.
[18] Owen, *ibid.*, 1934, **56**, 24.

Data from oxidation–reduction potentials are presented in Fig. 3, plotted for compactness on logarithmic scales. The linearity of the results, for a 30,000-fold variation in glycine anion concentration, indicates the formation of a 1 : 1 ferric–glycine complex and the absence of higher complexes. For the lower set of values in Fig. 3 perchloric acid was added progressively to a solution containing ferric ion and glycine, the limiting value of E, obtained at pH 0·6, being taken as E_0'. Subsequent calculation showed that the error from neglect of complex formation

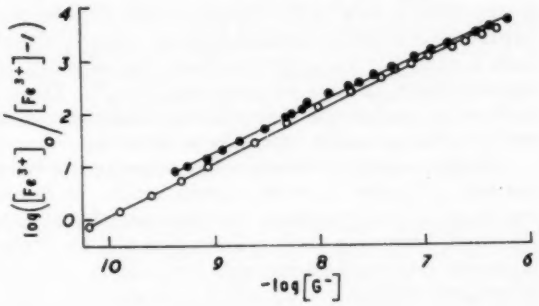

FIG. 3. *Glycine : ferric ion ratio and association constant of the complex, from oxidation–reduction potentials.*

Solid circles: ferric ion, 0·0017M; ferrous ion, 0·0014M; glycine, 0·8—1·0M; pH increased from 1·39 to 4·0.

Open circles: ferric ion, 0·0024M; ferrous iron, 0·0033M; glycine, 0·56—0·67M; pH decreased from 4·1 to 1·0.

at this pH was less than 1 mv. The upper set in Fig. 3 were obtained by measuring E_0' in an acid solution before the addition of glycine in perchloric acid; the pH of the solution was then increased by adding sodium hydroxide. The two values of E_0 so obtained were 0·4861 and 0·4956 v, respectively. If this small difference is due to the effect of glycine on the ferric and ferrous activity coefficients, as distinct from complex formation, the former value of E_0 should be used with both sets of results. This brings both lines in Fig. 3 very close together, with a maximum deviation, at the lowest values, of only 0·1 logarithmic unit, and leads to a stability constant for the complex of $\log K_1 = 10{\cdot}0$. Under the experimental conditions correction for hydrolysis of ferric ion was negligible.

Results obtained from spectrophotometry and plotted in Fig. 4 confirm the formation of a 1 : 1 ferric–glycine complex and lead to a value of $\log K_1 = 10{\cdot}2$ at 25°.

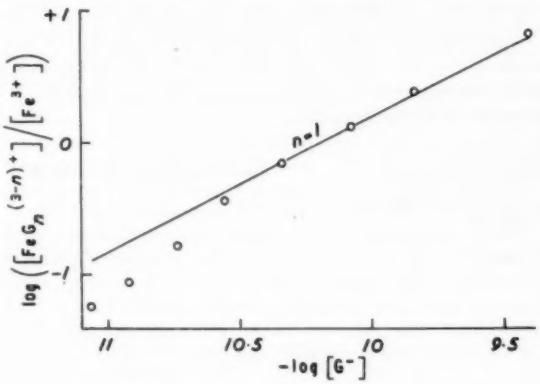

FIG. 4. *Spectrophotometric evaluation of glycine : ferric ion ratio and stability constant of complex.*

Data as for Fig. 2.

In Fig. 2 the slight drop in optical density between pH 2·4 and pH 3·3 is explained quantitatively by formation of the complex, $Fe_2(OH)_2^{4+}$, if the stability constant of the latter lies between the reported [16,17] values of $1{\cdot}2 \times 10^{-3}$ and $7{\cdot}3 \times 10^{-3}$ at 25°. This complex is more significant in these experiments than in the oxidation–reduction potential measurements because its concentration varied with the square of the ferric ion concentration. The rapid increase in optical density above pH 3·5 is believed to be due to the rapidly increasing concentration of colloidal ferric hydroxide, rather than to the formation of a higher ferric–glycine complex.

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Discussion

Spectrophotometric and oxidation–reduction potential measurements indicate that ferric ion forms a 1 : 1 complex with glycine. In view of the approximations involved, the two values obtained for the stability constant of the complex are in good agreement. The constancy of the value from oxidation–reduction potentials over a wide range of pH is surprising in view of the change of dielectric constant of glycine solutions with pH. Up to pH 4·5 the dielectric constant increases directly with the glycine zwitterion concentration[19] from a value not very different from that of water, the increase reaching a maximum of approximately 22 units per mole of glycine.[20] These changes should, from considerations such as are used in the Debye–Hückel treatment of ions in solution, exert a considerable effect on the activities, especially of ferric ion.

Similar complex formation has subsequently[21] been shown to occur between ferric ion and a number of other α-amino-acids. It is reasonable to assume that like other metal–amino-acid complexes the ferric complex is a chelate compound formed by binding the metal between a carboxylic oxygen and the amino-nitrogen atom. This assumption is supported by a comparison with the stability constants for metal derivatives of 8-hydroxyquinoline-5-sulphonic acid, where a comparable 5-membered ring is formed:

Values of $\log K_1$ *at* 20°.

Complexing species	Fe^{3+}	Cu^{2+}	Fe^{2+}
Glycine	10·0 [a]	8·5 [b]	4·3 [b]
8-Hydroxyquinoline-5-sulphonic acid	12·4 [c]	12·5 [b]	8·4 [b]

a = present work; *b* = ref. 13; *c* = present work, from oxidation–reduction potentials, I = 0·01—0·08.

A similar trend is also found for metal complexes with tetracycline, the corresponding values being[22] 9·9, 7·8, and 5·3: in this series the metal is presumably bound between two oxygen atoms. In all cases the stability of the ferric complex is close to, or somewhat greater than, that of the cupric complex, while the ferrous complex is 4 to 6 logarithm units less stable than the ferric one.

Because the solubility of ferric hydroxide is so low that, even in the presence of 1M-glycine, precipitation occurs from 0·01M-ferric perchlorate solutions above about pH 4·7, the maximum attainable concentration of glycine anion was very low. This is probably the reason why, although many bivalent cations form 1 : 2 and higher glycine complexes,[1,2] no evidence was obtained of ferric complexes of these types.

Department of Medical Chemistry,
The Australian National University, Canberra. [*Received, March 24th*, 1958.]

[19] Dunning and Shutt, *Trans. Faraday Soc.*, 1938, **34**, 479.
[20] Hedestrand, *Z. phys. Chem.*, 1928, **135**, 36.
[21] Perrin, following paper.
[22] Albert and Rees, *Nature*, 1956, **177**, 433.

633. *The Stability of Complexes of Ferric Ion and Amino-Acids.*

By D. D. Perrin.

Ferric ion and α-amino-acids form stable 1 : 1 complexes in acid solution. In most cases the stability constants obtained from oxidation–reduction potentials depend linearly on the basic ionisation constants of the amino-acids. Ferric complexes of glutamic acid, aspartic acid, and glycylglycine show increased stability because of additional chelation. Proline, hydroxyproline, and sarcosine complexes are less stable than predicted, possibly because of the difference in the amino-groups taking part in complex formation. Histidine is unusual in that complex formation takes place through the glyoxaline nitrogen atom instead of the α-amino-group. In the stability of its amino-acid complexes, ferric ion exceeds cupric ion and is comparable with mercuric ion.

Albert [1,2] and Perkins [3,4] have measured the stability of α-amino-acid complexes of a number of bivalent cations. Following the observation [5] that ferric ion and glycine form a 1 : 1-complex, we have studied the behaviour of a range of α-amino-acids with ferric ion. Except for cysteine,[6] where linkage appears to be through the sulphur atom, little direct evidence of complex formation between ferric ion and other α-amino-acids had previously been reported. Stability constants have been obtained for 1 : 1 ferric complexes with a range of naturally-occurring α-amino-acids and some related substances.

Experimental

Ferric and ferrous perchlorates were prepared as described previously.[5] The materials investigated were obtained from British Drug Houses Ltd. and Light and Co. Ltd. Arginine was prepared from arginine hydrochloride by ion-exchange on a column of Amberlite resin IRA-400. Ornithine hydrobromide was converted into the nitrate by double decomposition with silver nitrate. Purity was checked by paper chromatography with three solvent systems (*tert.*-butyl alcohol–formic acid–ethyl methyl ketone–water; collidine–lutidine–water; *n*-propyl alcohol–ammonia–water) followed by examination in ultraviolet light and staining with ninhydrin. Traces of other amino-acids (indicated in parentheses) were present in alanine (glycine), glutamic acid (leucine, valine), leucine (valine), methionine (serine or threonine), and proline (hydroxyproline) but did not appreciably affect estimates of the stability constants of the ferric complexes.

Except with histidine, which forms a slightly soluble perchlorate, all measurements were made in sodium perchlorate solutions of unit ionic strength at 20°. The ionisation constants of the amino-acids were obtained by potentiometric titration, with samples dried at 110°. Correction was made for hydrolysis. Where two ionisation constants of an amino-acid were close together they were evaluated by the method described by Britton.[7] All constants, which were expressed in terms of hydrogen activity as measured by glass electrode and of concentrations of amino-acid species, were consistent with published values. Oxidation–reduction potential and spectrophotometric measurements used in obtaining stability constants of the ferric complexes were made as described earlier.[5] Hedström's [8] values of the formation constants of the 1 : 1, 1 : 2, and 2 : 2 ferric–hydroxyl complexes were extrapolated to 20° and unit ionic strength from the results of Siddall and Vosburgh [9] and Mulay and Selwood [10] to give 7×10^{-4}, 4×10^{-7}, and 1×10^{-3}, respectively. These values were used in calculating the small corrections for hydrolysis of ferric ion.

[1] Albert, *Biochem. J.*, 1950, **47**, 531.
[2] *Idem, ibid.*, 1952, **50**, 690.
[3] Perkins, *ibid.*, 1952, **51**, 487.
[4] *Idem, ibid.*, 1953, **55**, 649.
[5] Perrin, preceding paper.
[6] Cannon and Richardson, *Biochem. J.*, 1929, **23**, 1242; Tanaka, Kolthoff, and Stricks, *J. Amer. Chem. Soc.*, 1955, **77**, 1996, 2004.
[7] Britton, "Hydrogen Ions," Chapman and Hall, London, 4th edn., 1955, vol. 1, p. 217.
[8] Hedström, *Arkiv Kemi*, 1953, **5**, 457; 1953, **6**, 1.
[9] Siddall and Vosburgh, *J. Amer. Chem. Soc.*, 1951, **73**, 4270.
[10] Mulay and Selwood, *ibid.*, 1955, **77**, 2693.

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As discussed [5] for ferric complex formation with glycine, it is reasonable to assume that with most α-amino-acids the ferric complex results from chelation of the metal ion by the amino-acid anion in which the amino-group is not ionised. Results here reported confirm the general correctness of this assumption. Unless otherwise indicated, all stability constants are calculated for this direct reaction.

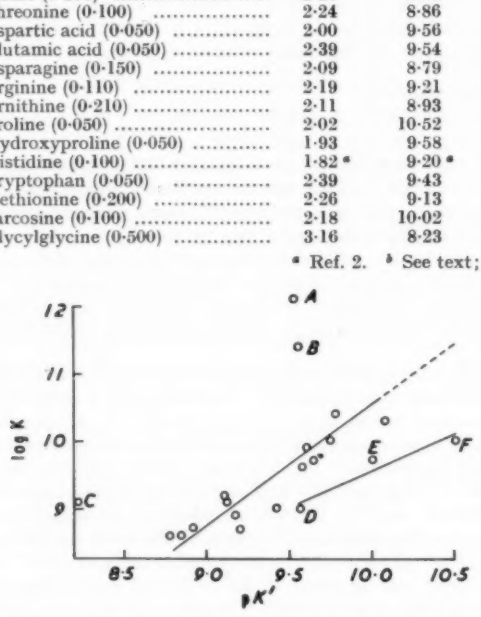
Results and Discussion

Values of log K for the 1 : 1 ferric–amino-acid complexes, obtained from oxidation–reduction potentials, are listed in the Table, together with relevant experimental details.

Stability constants of 1 : 1 *ferric–amino-acid complexes at* 20° *and unit ionic strength.*

	Ionisation constants			log K	
Amino-acid (M)	α-CO_2H	α-NH_2	Other	± S.E. (no. of obs.)	pH
Glycine (for comparison)	2·41	9·76	—	10·0	—
Alanine (1·00)	2·49	9·79	—	10·4 ± 0·03 (17)	0·77—3·35
α-Amino-*n*-butyric acid (0·300)	2·31	9·66	—	9·7 ± 0·01 (11)	1·54—3·17
α-Amino*iso*butyric acid (0·500)	2·48	10·09	—	10·3 ± 0·03 (9)	1·79—3·06
Valine (0·300)	2·38	9·59	—	9·6 ± 0·02 (14)	1·26—3·21
Leucine (0·200)	2·37	9·62	—	9·9 ± 0·02 (10)	1·45—2·98
β-Phenylalanine (0·150)	2·21	9·18	—	8·9 ± 0·03 (9)	1·47—2·66
Serine (0·300)	2·26	9·12	—	9·2 ± 0·04 (11)	1·32—2·73
Threonine (0·100)	2·24	8·86	—	8·6 ± 0·03 (9)	1·38—2·56
Aspartic acid (0·050)	2·00	9·56	3·78	11·4 ± 0·03 (10)	1·64—2·27
Glutamic acid (0·050)	2·39	9·54	4·21	12·1 ± 0·02 (8)	1·56—2·33
Asparagine (0·150)	2·09	8·79	—	8·6 ± 0·01 (8)	1·52—2·40
Arginine (0·110)	2·19	9·21	(12·5 [a])	8·7 ± 0·03 (9)	1·62—2·62
Ornithine (0·210)	2·11	8·93	10·59	8·7 ± 0·05 (7)	1·76—2·85
Proline (0·050)	2·02	10·52	—	10·0 ± 0·03 (9)	1·62—2·55
Hydroxyproline (0·050)	1·93	9·58	—	9·0 ± 0·03 (8)	1·70—2·48
Histidine (0·100)	1·82 [a]	9·20 [a]	6·08 [a]	4·7 [b] ± 0·04 (7)	1·80—2·92
Tryptophan (0·050)	2·39	9·43	—	9·0 ± 0·03 (10)	1·82—2·92
Methionine (0·200)	2·26	9·13	—	9·1 ± 0·02 (9)	1·49—2·85
Sarcosine (0·100)	2·18	10·02	—	9·7 ± 0·03 (9)	1·73—2·79
Glycylglycine (0·500)	3·16	8·23	—	9·1 ± 0·05 (7)	1·37—3·03

[a] Ref. 2. [b] See text; $I = 0·1$.



Dependence of stability constant of ferric complex on basic ionisation constant of amino-acid.

Anomalous acids:
A, glutaminic acid.
B, aspartic acid.
C, glycylglycine.
D, hydroxyproline.
E, sarcosine.
F, proline.

The correction for hydrolysis of ferric ion was less than $0·05 \times \{([Fe^{3+}]_0 - [Fe^{3+}])/[Fe^{3+}]\}$ for all amino-acids except proline, hydroxyproline, and tryptophan (less than 0·10 ×) and histidine (less than 0·25 ×). The rapid increase in magnitude of this correction with increase in pH and the insolubility of ferric hydroxide set an upper limit to the accessible range of pH. The rapid fall of anion concentration with decrease in pH determined the lower limit at which significant differences in free ferric ion concentration could be measured.

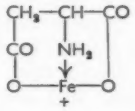
Except for histidine, all amino-acids gave consistent values of log K over the experimental range of pH. As with glycine, no evidence of higher complex formation was found.

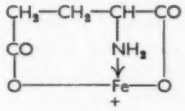
For the combination of a cation with a series of similar ligands Bjerrum [11] found log

[11] Bjerrum, *Chem. Rev.*, 1950, **46**, 381.

$K = \alpha\, pK' + c$, where α and c were constants, and K' was the ionisation constant of the ligand. If the factors governing the binding of protons and ferric ions by amino-acid anions are similar, Bjerrum's equation should apply to the present results. Although such a treatment is a considerable over-simplification, the Figure shows that for most of the acids studied a roughly linear relation is, in fact found between log K and the appropriate pK', with $\alpha = 1{\cdot}8$ and $c = -7{\cdot}5$.

Aspartic and glutamic acids do not fit this relation. The much greater than predicted stabilities of their ferric complexes (by 1·8 and 2·5 log units) probably indicate the formation of terdentate complexes involving the additional carboxyl group. The possibility that only the two carboxyl groups or the β- or γ-carboxyl and the amino-group take part in complex formation was not supported by the experimental results. Values of the stability constants calculated on these assumptions varied considerably with pH. Atomic models (Courtaulds) of aspartic and glutamic acids showed that the terdentate structures (I)

(I) 

 (II)

and (II) should be possible and suggested that the somewhat lower stability of the ferric–aspartic acid complex was due to steric effects. For an ionic radius of 0·60 Å,[12] formation by aspartic acid of a second, six-membered, ring between ferric ion and a β-carboxylic oxygen atom would involve some strain owing to the bond directions. With glutamic acid the decrease in stability of the ferric complex that would be expected from the increase in ring size is apparently more than offset by the removal of this strain. Results for ferric ion differ from those for bivalent cations where, in most cases, the stability of the 1 : 2 glutamic acid complex is appreciably less than that of the 1 : 2 aspartic acid complex and is comparable with the value for glycine.[2,4] The ferric complex of asparagine (the β-amide of aspartic acid) does not show enhanced stability. This result is in line with the known weakness of the amide group in chelation.

The ferric complexes with proline, hydroxyproline, and sarcosine are all less stable than predicted from results for other amino-acids (by 1·4, 0·7, and 0·8 log unit). However, as the alkyl group they contain in place of one of the amino-hydrogen atoms probably gives rise to a steric effect in complex formation, these three acids should be considered as members of a related, but distinct, series of ligands.

For most of the remaining ferric–amino-acid complexes, the greatest single factor governing their stability appears to be the basic ionisation constant of the amino-acid. The low values of this constant for serine, threonine, and asparagine may be due either to inductive effects or to the formation of hydrogen bonds between the carboxylic oxygen and the β-hydroxyl or the amide group. The depression of pK' produced by introducing the hydroxyl or amide group is similar to that found in comparing 2-aminoethanol with ethylamine.[13]

The terminal basic groups in arginine and ornithine do not appear to take part in ferric complex formation. On the other hand, when the stability constant of the ferric–histidine complex was calculated for complex formation involving the α-amino- and the carboxyl group no constancy was found, values of log K changing by one unit for a change of one pH unit. This was also true for calculations where complex formation was assumed to take place through the glyoxaline-nitrogen atom and the α-amino-group, by analogy with complexes with some bivalent cations.[2] A steady value of the stability constant was obtained, however, if ferric ion was assumed to be bound between the glyoxaline-nitrogen

[12] Pauling, "The Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, New York, 1939, p. 330.
[13] Bruehlam and Verhoek, *J. Amer. Chem. Soc.*, 1948, **70**, 1401.

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atom and the carboxyl group, the α-amino-group remaining ionised. The weakness of the 7-membered ring formed in this way is shown by the low value of the stability constant.

Attempts to measure the stability constant of a ferric–cysteine complex in acid solution were unsuccessful; reduction of ferric ion by cysteine was very rapid. No difficulties were encountered with methionine.

Results for glycylglycine showed the ferric complex to be formed by linkage through the amino- and the carboxyl group as in simple amino-acids. So large a ring structure would not be very stable but chelation also probably occurs through the amide group, giving rise to a terdentate structure containing two 5-membered rings.[14] Hence, although the amide group is only a weak donor, and the stability constant of the complex is less than for ferric–glycine, the complex is 1·8 log units more stable than would be expected for an amino-acid of the same pK'.

All ferric–amino-acid complexes were amber-coloured. The absorption spectra of the aspartic and glutamic acid complexes resembled closely the ferric–glycine spectrum. Most of the other amino-acid complexes showed little or no evidence of the maximum near 460 mμ but only a general absorption increasing steadily towards the blue end of the spectrum. As an approximate check on the value found from oxidation–reduction potentials for the stability constant of the ferric–glutamic acid complex, estimates were obtained by measuring the dependence of optical density on pH. The approximate constancy, around pH 3, of the optical density of a solution containing ferric ion (0·0083M) and glutamic acid (0·0500M) was assumed to be due to complete complex formation. The measured optical densities, over the range pH 1·36—1·99 at 25° and $I = 1$, gave log $K = 12{\cdot}4$ (range 12·1—12·7). The calculation was very sensitive to errors in pH or pK'; the maximum deviation in log K could be caused by an error of 0·1 pH unit. Similar measurements between pH 1·27—1·87 gave for the ferric–aspartic acid complex a value of log $K = 11{\cdot}5$ (range 11·3—11·6). For both acids these results confirm the more accurate values obtained from oxidation–reduction potentials.

The approximate relation,[1] log $K_1 = \frac{1}{2}$ (log $K_3 - 1$), where K_3 is the stability constant of the 1 : 2-complex, enables published data on amino-acid complexes with bivalent cations to be compared with the present results. From these results it appears that in relation to Mellor and Maley's [15] series of bivalent metals, ferric ion should be placed well above cupric ion [1,2] and near mercuric ion.[3,4]

By analogy with bivalent cations, 1 : 2 and 1 : 3 ferric complexes might be expected. However, under our conditions no evidence of complexes higher than 1 : 1 was obtained.

The ionisation constants used in this work were determined by Mr. F. Robinson, whom the author thanks.

Department of Medical Chemistry,
The Australian National University, Canberra. [*Received, March 24th*, 1958.]

[14] Martell and Calvin, "Chemistry of the Metal Chelate Compounds," Prentice-Hall, New York, 1952, p. 139.
[15] Mellor and Maley, *Nature*, 1948, **161**, 436.

634. *The Preparation of Optically Active Phosphorus Compounds.*

By M. Green and R. F. Hudson.

The syntheses of methyl methyl-1-naphthylphosphinate, methyl 1-naphthyl methylphosphonate, and *S*-benzyl methyl-3-phenanthrylphosphinothiolate are described. The last two esters have been partially resolved by means of their complexes with (−)-α-(2 : 4 : 5 : 7-tetranitro-9-fluorenylideneamino-oxy)propionic acid.

Few optically active phosphorus compounds had been prepared until recently, owing to difficulty in crystallising the mixed diastereoisomers. Thus, in the resolution of phosphine oxides Meisenheimer *et al.*[1] found that crystallisation required several months. More progress has been made recently by incorporating well-defined acidic or basic groups into the asymmetric phosphorus compound. On this basis, Mann and his collaborators [2] resolved phosphonium salts; Aaron and Miller [3] resolved thiolic acids by conventional methods. Coyne, McEwen, and VanderWerf [4] resolved a phosphinic ester (I) containing quaternary ammonium groups, using (+)- and (−)-tartaric acid as resolving agents. On concentrating solutions of the (−)-di-*O*-benzoyltartrate of the ester in methanol, we obtained a thick syrup, and only 0·9 g. of pure (−)-methiodide was isolated from 120 g. of the racemate. Attempts to resolve compound (I) by reaction with silver α-bromo-π-camphorsulphonate or 10-camphorsulphonate also gave syrups; though crystals of the α-bromo-π-camphorsulphonate were obtained after 3 months by allowing the syrup to stand over phosphoric oxide in a vacuum-desiccator, no separation of the diastereoisomer was achieved. Attempted asymmetric solvation [5] of compound (I) by ethyl (+)-tartrate induced no optical activity in the ester.

$Me_3\overset{+}{N}\cdot C_6H_4\cdot PMeO\cdot OMe$

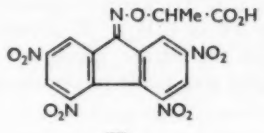
(I)

$1\text{-}C_{10}H_7\cdot PMeO\cdot OMe$

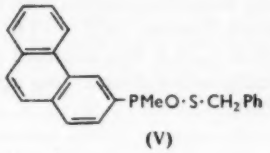
(III)

$1\text{-}C_{10}H_7\cdot O\cdot PMeO\cdot OMe$

(IV)



(II)



(V)

Newman and Lutz [6] introduced a method whereby a molecular complex is formed between an asymmetric compound containing a condensed aromatic nucleus and optically active α-(2 : 4 : 5 : 7-tetranitro-9-fluorenylideneamino-oxy)propionic acid (II), the acidic component being later removed by treatment with aqueous sodium hydrogen carbonate. We tried this method first with methyl methyl-1-naphthylphosphinate (III). Attempts to link the naphthyl group directly to the phosphorus atom by the Grignard reaction between 1-naphthylmagnesium bromide and *NN*-diethylmethylphosphonochloridamidate were abandoned as the product was contaminated with a large amount of naphthalene. An alternative route starting with phosphorus trichloride and the aryl cadmium,[7] prepared by the action of cadmium chloride on the Grignard reagent, was used to prepare methyl-1-naphthylphosphinic acid in 25% yield.

The methyl ester (III) did not form an addition compound with the acid (II), probably on account of steric hindrance between the oxygen atoms of the ester and the nitro-groups. Since Newman and Lutz [6] successfully resolved *sec.*-butyl 1-naphthyl ether by this method,

[1] Meisenheimer and Lichtenstadt, *Ber.*, 1911, **44**, 356; Meisenheimer, *Annalen*, 1926, **449**, 2136.
[2] Holliman and Mann, *J.*, 1947, 1634; Hart and Mann, *J.*, 1955, 4107.
[3] Aaron and Miller, *J. Amer. Chem. Soc.*, 1956, **78**, 3538.
[4] Coyne, McEwen, and VanderWerf, *ibid.*, p. 3061.
[5] Buchanan, *J.*, 1950, 500; Turner and Harris, *J.*, 1950, 1753.
[6] Newman and Lutz, *J. Amer. Chem. Soc.*, 1956, **78**, 2469.
[7] Fox, *ibid.*, 1950, **72**, 4147.

XUM

methyl 1-naphthyl methylphosphonate (IV), which similarly has an oxygen atom between the aromatic system and the asymmetric centre, was prepared from methylphosphonic dichloride through the intermediate methyl methylphosphonochloridate. Attempts to prepare the ester (IV) by way of 1-naphthyl methylphosphonochloridate were unsuccessful, indicating that the naphthyloxy-group is replaced in preference to the chlorine atom by one equivalent of alkoxide ions and suggesting that the substitution is controlled by steric interaction between the naphthyl group and the alkoxide ion. The ester (IV) readily formed a complex with tetranitrofluorenone and with the acid (II), from which a partially resolved, dextrorotatory ester was obtained. An attempt to isolate the lævorotatory ester was unsuccessful.

In order to prepare an ester with one replaceable group only and with the condensed aromatic system attached directly to the phosphorus atom, the phosphinothiolate (V) was prepared from 3-iodophenanthrene, itself synthesised by Bachmann's method.[8] This ester was chosen as it is the least sterically hindered phenanthryl derivative, and also because it was expected to be a solid. The ester (V) was synthesised by using the aryl-

$$\text{LiPh} + \text{MePOCl}\cdot\text{NEt}_2 \longrightarrow \text{MePhPO}\cdot\text{NEt}_2 \xrightarrow{\text{HCl}} \text{MePhPO}_2\text{H} \xrightarrow{\text{SOCl}_2} \text{MePhPOCl} \longrightarrow \text{MePhPO}\cdot\text{OMe}$$

lithium compound [9] in the first stage. According to Willans,[10] lithium aryls are much more reactive towards phosphonate esters than are Grignard compounds, and they have been used successfully for replacing chlorine in dialkyl phosphorochloridates [11] [attention has already been drawn to the difficulty experienced in the preparation of compound (III) from the Grignard reagent]. As a preliminary, methyl methylphenylphosphinate was prepared in 25% yield from phenyl-lithium by the annexed route. The same procedure was used to prepare *S*-benzyl methyl-3-phenanthrylphosphinothiolate (V), the phosphinyl chloride being treated with toluene-ω-thiol and pyridine in ether in the final stage. This ester readily formed a complex with the acid (II), and its regeneration therefrom gave a dextrorotatory fraction, $[\alpha]_D^{20}$ +17·0° (*c* 3·0 in C_6H_6). A lævorotatory fraction, $[\alpha]_D^{20}$ −13·1° (*c* 2·0 in C_6H_6), was obtained from the filtrate, giving a total recovery of 90% in these optically active forms. No attempt was made to obtain optically pure isomers by this method.

Experimental

p-Dimethylaminophenyldichlorophosphine, prepared (15% yield) by Michaelis and Schenk's method,[12] had b. p. 158—160°/0·6 mm. The following esters were prepared as described by Coyne, McEwen, and VanderWerf: [4] *p*-dimethyl dimethylaminophenylphosphonite, b. p. 125—126°/0·4 mm. (40%) (Found: C, 56·5; H, 7·7; N, 6·5. Calc. for $C_{10}H_{16}O_2NP$: C, 56·3; H, 7·6; N, 6·6%); methyl *p*-dimethylaminophenylmethylphosphinate, b. p. 170—172°/0·4 mm., m. p. 81° (Found: C, 56·0; H, 7·6; N, 6·5. Calc. for $C_{10}H_{16}O_2NP$: C, 56·3; H, 7·6; N, 6·6%); methyl *p*-dimethylaminophenylmethylphosphinate methiodide (as I), m. p. 159—160° (Found: I, 34·20. Calc. for $C_{11}H_{19}O_2NPI$: 34·3%).

Resolution of the Iodide (I).—(*a*) Silver camphor-10-sulphonate (3·38 g.) and the iodide (3·73 g.) in absolute methanol (10 ml.) were boiled for 10 min., and the silver iodide was then filtered off. No crystals were obtained on cooling, and slow evaporation gave a thick syrup. (*b*) α-Bromo-π-camphorsulphonic acid was prepared [13] from α-bromocamphor, itself prepared by Kipping and Pope's method.[14] The ammonium salt was obtained as needles, m. p. 269°. The resolution was attempted in the same way as above, and only a syrup was obtained after 3 months' storage over P_2O_5.

[8] Bachmann, *J. Amer. Chem. Soc.*, 1936, **58**, 2097, 2195.
[9] Freedman and Doak, *Chem. Rev.*, 1957, 479.
[10] Willans, *Chem. and Ind.*, 1957, 243.
[11] Burger and Dawson, *J. Org. Chem.*, 1951, **16**, 1250.
[12] Michaelis and Schenk, *Ber.*, 1888, **21**, 1497; *Annalen*, 1890, **260**, 1.
[13] Pope and Read, *J.*, 1914, **105**, 801.
[14] Kipping and Pope, *J.*, 1893, **63**, 576.

(*c*) D(−)-Di-*O*-benzoyltartaric acid (m. p. 88—89°, $[\alpha]_D^{20}$ −113·5°; lit.,[15] m. p. 87—89°, $[\alpha]_D^{20}$ −114·8°) was prepared from the anhydride (m. p. 188—189°, $[\alpha]_D^{20}$ −156°; lit.,[15] m. p. 173°, $[\alpha]_D^{20}$ −142°) by Butler and Cretcher's method.[15] The acid (72·5 g.), suspended in distilled water (2·2 l.) containing ammonia (176 ml. of 1·14N), was heated at 90°, and silver nitrate (34 g.) was added. After cooling, the white crystalline precipitate was filtered off and washed with water (50 ml.). The silver D(−)-di-*O*-benzoyltartrate (50 g.) was dried in a vacuum-desiccator. This salt (88 g.) and the iodide (I) (120 g.) were refluxed in methanol (240 ml.) for 10 min., and the quantitative amount of silver iodide filtered off. The solution was cooled, yielding 70 g. of crystals, m. p. 120—121° (lit., m. p. 116—119°), $[\alpha]_D^{25}$ −80° (in MeOH). The partially resolved material was recrystallised seven times from methanol, to give 7·1 g. of solid, m. p. 139°, $[\alpha]_D^{25}$ −90° (in MeOH). No further crystals could be obtained on evaporation of the filtrates.

The pure diastereoisomer (7·1 g.) in 95% ethanol (40 ml.) was added to a solution of potassium iodide (2 g.) in 95% ethanol (40 ml.). The solution was boiled for 5 min., and the potassium D(−)-di-*O*-benzoyltartrate was then filtered off. After 24 hr., 4 g. of the methiodide, m. p. 146—149°, had crystallised. This was recrystallised five times from ethanol, giving 0·9 g. of the (−)-methiodide, m. p. 156°, $[\alpha]_D^{25}$ −28·7° (Found: C, 37·6; H, 5·2; N, 4·0; P, 9·0; I, 35·7. Calc. for $C_{11}H_{13}O_3NIP$: C, 37·2; H, 5·4; N, 3·95; P, 8·70; I, 35·7%).

NN-*Diethylmethylphosphonochloridamidate.*—Diethylamine (7·3 g.) and triethylamine (10·1 g.) in ether (50 ml.) were added with stirring and cooling to a solution of methanephosphonyl dichloride (13·3 g.) in ether (100 ml.). The mixture was stirred for 1 hr. and the amine hydrochloride filtered off. The ether was removed and the residue fractionally distilled, to yield NN-*diethylmethylphosphonochloridamidate* (17 g.), b. p. 80°/2 mm., n_D^{17} 1·4678 (Found: C, 35·4; H, 7·5; N, 8·3; P, 18·1; Cl, 20·9. $C_5H_{13}ONClP$ requires C, 35·4; H, 7·7; N, 8·3; P, 18·3; Cl, 20·7%).

α-*Naphthyldichlorophosphine.*—α-Bromonaphthalene (414 g.) in dry ether (500 ml.) was added slowly to magnesium (48·5 g.) in ether (500 ml.). When the reaction had ceased, anhydrous cadmium chloride (183·4 g.) suspended in ether (400 ml.) was added. The mixture was stirred for 2 hr., then added slowly with stirring to phosphorus trichloride (274·5 g.) in ether (1 l.) at −30°. The mixture was allowed to reach room temperature, and after 12 hr. the solid was filtered off and washed with ether. The solvent was removed on the water-bath and the residue distilled, to give α-*naphthyldichlorophosphine* (25%), b. p. 118—120°/0·5 mm., m. p. 54° (Found: C, 52·6; H, 3·0; P, 13·7; Cl, 30·0. $C_{10}H_7PCl_2$ requires C, 52·5; H, 3·1; P, 13·6; Cl, 30·7%).

Dimethyl α-*Naphthylphosphonite.*—α-Naphthyldichlorophosphine (37 g.) in dry ether (100 ml.) was added with stirring to methanol (30 g.) and diethylaniline (48·2 g.) in ether (200 ml.) at 0°. The mixture was stirred for 2 hr. and the amine hydrochloride then filtered off. The ether was removed on the water-bath and the residue fractionally distilled, to give *dimethyl* α-*naphthylphosphonite*, b. p. 101°/0·15 mm., n_D^{20} 1·6127 (Found: C, 64·9; H, 5·7; P, 14·1. $C_{12}H_{13}O_3P$ requires C, 65·2; H, 5·9; P, 14·1%).

*Methyl Methyl-*α-*naphthylphosphinate.*—Dimethyl α-naphthylphosphonite (23 g.) and methyl iodide (2 ml.) in benzene (50 ml.) were heated on a water-bath for 24 hr. After removal of the solvent, distillation gave *methyl methyl-*α-*naphthylphosphinate* (18%), b. p. 128—130°/0·1 mm. (Found: C, 65·6; H, 5·8; P, 14·0. $C_{12}H_{13}O_2P$ requires C, 65·2; H, 5·9; P, 14·1%).

The ester (0·55 g.) and 2 : 4 : 5 : 7-tetranitrofluorenone (0·87 g.) were separately dissolved in the minimum quantity of hot glacial acetic acid. No colour was produced on mixing the solutions and, on cooling, tetranitrofluorenone, m. p. 254° (from acetic acid), was obtained.

α-*Naphthyl Methylphosphonochloridate.*—α-Naphthol (48 g.), diethylaniline (49·7 g.), and methylphosphonyl dichloride (44·3 g.) were heated for 4 hr. in sodium-dried benzene (200 ml.). After removal of the benzene, ether was added, and the precipitated diethylaniline hydrochloride filtered off. Fractional distillation of the filtrate gave the *chloridate* (61·5 g.), b. p. 142—144°/0·1 mm., m. p. 46—47° (Found: C, 55·0; H, 4·2; P, 12·3; Cl, 14·9. $C_{11}H_{10}O_2ClP$ requires C, 54·7; H, 4·3; P, 12·9; Cl, 14·4%).

A solution of sodium (3·9 g.) in methanol (100 ml.), added at 0° to this ester (40·7 g.) in ether (200 ml.), gave dimethyl methylphosphonate, b. p. 50°/0·1 mm., n_D^{20} 1·4136, and α-naphthol, m. p. 94° (picrate, m. p. 187°).

Methyl α-*Naphthyl Methylphosphonate.*—Methyl methylphosphonochloridate (39·9 g.) was

[15] Butler and Cretcher, *J. Amer. Chem. Soc.*, 1933, **55**, 2605.

added with stirring to a suspension of sodium methoxide (5·1 g. of sodium in 100 ml. of alcohol) and α-naphthol (31·9 g.) in benzene (500 ml.) at 0°. After removal of the benzene and alcohol, ether was added and the sodium chloride filtered off. The *ester* (15·5 g.) obtained by fractional distillation had b. p. 128—130°/0·1 mm., n_D^{20} 1·5807 (Found: C, 60·8; H, 5·5; P, 13·0. $C_{12}H_{13}O_3P$ requires C, 60·5; H, 5·4; P, 13·0%).

Resolution. A brick-red complex (m. p. 124°) was obtained on mixing solutions of the ester and 2 : 4 : 5 : 7 tetranitrofluorenone in 1 : 1 propionic acid–light petroleum. A similar *complex* (Found: C, 50·1; H, 3·1; N, 10·1; P, 4·6. $C_{28}H_{22}O_{14}N_5P$ requires C, 49·3; H, 3·1; N, 10·3; P, 4·5%) was obtained with the (−)-form (m. p. 112°) of the resolving agent. Methyl α-naphthyl methylphosphonate (4·7 g.) and (−)-α-(2 : 4 : 5 : 7-tetranitro-9-fluorenylideneamino-oxy)-propionic acid (9·0 g.) were dissolved in hot 1 : 1 propionic acid–light petroleum (b. p. 60—80°). Three portions of light petroleum (10 ml.) were added to the cold solution, giving three fractions of complex. The solid was filtered off and dried in a vacuum-desiccator for 24 hr.

The molecular complex (10 g.), suspended in ether (200 ml.), was treated with saturated sodium hydrogen carbonate solution (100 ml.) and then with dilute sodium hydrogen carbonate solution (2 × 100 ml.). The combined extracts were treated with ether (5 × 100 ml.), and the combined ether solutions were dried ($MgSO_4$). Removal of the ether and distillation gave the active *ester* (2·0 g.), b. p. 116—118°/10^{-3} mm., n_D^{20} 1·5813, $[\alpha]_D^{20}$ +44° (*c* 1·5 in dioxan) (Found: C, 60·5; H, 5·5; P, 13·0. $C_{12}H_{13}O_3P$ requires C, 60·5; H, 5·4; P, 13·0%). The filtrates obtained from the initial precipitation were treated with sodium hydrogen carbonate solution as described above, and the aqueous solution was extracted with ether. The yield of (−)-ester was too small to be distilled satisfactorily.

Chromatographic Separation of Methyl α-Naphthyl Methylphosphonate.—The complex (0·12 g.) in benzene (100 ml.) was placed on an alumina column, and eluted with benzene. The complexing acid was strongly absorbed. Separation of the α-naphthyl ester was followed by its fluorescence in ultraviolet light. The benzene was removed by continuous azeotropic distillation with spectroscopically pure ethanol. The ethanol solution (25 ml.) had α 0·13° in a 1 dm. tube. The ester was characterised spectroscopically ($\lambda_{max.}$ 254·5 mμ, $\lambda_{min.}$ 245 mμ).

Methyl Methylphenylphosphinate.—The concentration of active phenyl-lithium in ether, prepared by Gilman's method,[16] was estimated by titration of an aliquot part in water with hydrochloric acid, and by adding a second part to benzyl chloride (2 ml.) in ether (10 ml.) and titration in water after 4 min.

NN-Diethylmethylphosphonochloridamidate (4 g.) in ether (100 ml.) was added with stirring to phenyl-lithium (2·0 g.) in ether (101 ml.) at 0°. The mixture was stirred for 1 hr., the ether removed, and concentrated hydrochloric acid (500 ml.) added. After 3 hours' boiling, methylphenylphosphonic acid was extracted with ether, dried, recovered, and allowed to solidify. The acid in hot benzene (50 ml.), was heated for 6 hr. with an excess of thionyl chloride. After the removal of thionyl chloride and benzene, the residue was boiled for 1 hr. with an excess of methanol and pyridine. The mixture was poured into water (200 ml.), and an ether extract of it dried ($MgSO_4$). *Methyl methylphenylphosphinate* obtained by fractional distillation (25%) had b. p. 83—85°/0·1 mm. (Found: C, 62·1; H, 7·4; P, 20·0. $C_9H_7O_2P$ requires C, 62·4; H, 7·4; P, 20·0%).

S-*Benzyl Methyl-3-phenanthrylphosphinothiolate.*—*n*-Butyl-lithium in ether (48 ml.; 0·925M) was added at 6—20° to 3-iodophenanthrene [8] (12·2 g.) in ether (200 ml.). The temperature was then allowed to rise, and *NN*-diethylmethylphosphonochloridamidate (6·8 g.) in ether (50 ml.) added dropwise. The mixture was stirred for 2 hr., boiled for 10 min., and evaporated. The residue was boiled with concentrated hydrochloric acid (200 ml.) for 1½ hr., cooled, and continuously extracted with ether for 4 hr. The ether solution was dried ($MgSO_4$) the solvent removed, and the residue dissolved in benzene (100 ml.). The solution was heated for 6 hr. with an excess of thionyl chloride. After removal of the benzene and thionyl chloride under reduced pressure, a slight excess of toluene-ω-thiol and of pyridine was added. Ether (100 ml.) was next added and the mixture boiled for 2 hr., then poured into water (250 ml.). The ether layer was dried ($MgSO_4$) and fractionally distilled. The fraction of b. p. 136—142°/0·2 mm. solidified and recrystallised from ethanol, to give the *ester*, m. p. 69° (4·2 g.) (Found: C, 72·1; H, 5·41; S, 8·9; P, 8·01. $C_{22}H_{19}OSP$ requires C, 72·8; H, 5·23; S, 9·09; P, 8·54%). It formed a molecular complex, m. p. 195°, with 2 : 4 : 5 : 7-tetranitrofluorenone.

[16] Gilman, "Organic Reactions," Wiley, Vol. VIII, p. 286.

Resolution. The ester (4·2 g.) was added to the propionic acid resolving agent (5·2 g.) in glacial acetic acid (50 ml.). The dark yellow complex was filtered off and dried in a vacuum-desiccator, the filtrate being retained. The same procedure was then followed as described above for methyl α-naphthyl methylphosphonate. Recrystallisation from ethanol gave the active ester (2·0 g.), m. p. 67°, $[\alpha]_D^{20}$ +17° (*c* 1·7 in C_6H_6). Treatment of the acetic acid filtrate with aqueous sodium hydrogen carbonate solution yielded, after recrystallisation from ethanol, the lævorotatory ester (1·73 g.), m. p. 69·5°, $[\alpha]_D^{20}$ −13·1° (*c* 2·0 in C_6H_6).

Optical activity measurements were made on a Hilger microptic polarimeter, and the analyses carried out by The Chemistry Department of Imperial College, London.

QUEEN MARY COLLEGE (UNIVERSITY OF LONDON),
MILE END ROAD, LONDON, N.1. [*Received, February 21st*, 1958.]

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635. *The Halides of Niobium (Columbium) and Tantalum. Part V.* Diethyl Ether Complexes of the Pentachlorides and Pentabromides; the Solubility of Tantalum Pentaiodide in Ether.*

By ALAN COWLEY, FRED FAIRBROTHER, and NORMAN SCOTT.

Crystalline 1 : 1 complexes between diethyl ether and $NbCl_5$, $TaCl_5$, $NbBr_5$, and $TaBr_5$ have been prepared, and their compositions established by analysis and vapour-pressure measurements. TaI_5 does not form an ether complex. The solubilities of the pentachlorides and pentabromides in ether are greater than the ideal: that of TaI_5 is less.

The complexes decompose at about 100° into ethyl halide and metal oxytrihalide. The oxytrihalides disproportionate at higher temperatures into pentoxide and pentahalide.

NIOBIUM and tantalum pentafluorides [1] and pentachlorides [2] are Friedel–Crafts-type catalytic metal halides. We now find that tantalum pentachloride and both pentabromides are also. These halides are therefore electron acceptors or Lewis acids, and should form addition compounds with ethers, although no such compounds appear to have been described. These ether complexes are relevant to the general chemistry of these metals and in particular to their co-ordination with oxygen, which dominates it in aqueous systems.

We have examined the interaction between the pentachlorides and pentabromides and diethyl ether and in each case isolated a stable crystalline 1 : 1 complex with a dissociation pressure, at 16°, of less than 1 cm. Hg.

We were unable to find any evidence of complex formation between ether and tantalum pentaiodide, nor does this halide appear to possess any significant Friedel–Crafts-type catalytic activity; whereas the solubility of the pentachlorides and the pentabromides is greater than ideal, that of tantalum pentaiodide is less.

Pyrolysis of the ether complexes splits the ether at temperatures near 100° with the formation of ethyl halide and metal oxytrihalide, the latter disproportionating at higher temperatures into the pentahalide and pentoxide.

We approached the problem both by the study of the temperature variation of the solubility of the halides in ether and by the measurement of the vapour pressure of ether–halide systems.

EXPERIMENTAL

Preparation of Halides.—Niobium pentachloride was prepared from the pure metal sheet and dry chlorine at 300—350°, as described by Alexander and Fairbrother.[3] Tantalum pentachloride was prepared by passing dry hydrogen chloride over the metal sheet at 350—400°. The

* Part IV, *J.*, 1954, 1031.

[1] Fairbrother and Frith, *J.*, 1951, 3051.

[2] Grosse and Ipatieff, *J. Org. Chem.*, 1937, **1**, 559; Dermer and Billmeier, *J. Amer. Chem. Soc.*, 1942, **64**, 464.

[3] Alexander and Fairbrother, *J.*, 1949, S223.

bromides were very conveniently prepared, in excellent yield and free from hydrolysis products, by the following technique. About 5 g. of sheet metal were placed in a silica boat in the tube shown in Fig. 1, and an excess of dry bromine run into the end limb through *C*, which was then sealed off. The bromine was degassed and then solidified in liquid air, and the rest of the tube heated and evacuated through *D*, which was then sealed off. The section *A–B* was heated to 400—450°, and the bromine allowed to warm to room temperature. Reaction proceeded smoothly, the bromide condensing in the sealed end *E*.

Tantalum pentaiodide was prepared as described by Alexander and Fairbrother [4] from iodine vapour and a cylinder of the metal, heated in an induction furnace. The halides were all purified by five or six fractional sublimations *in vacuo* and finally sublimed into fragile hook-ended ampoules.

Ether.—Anæsthetic ether was distilled from one-fifth of its volume of sulphuric acid, kept over phosphoric oxide for at least a week, decanted, fractionated under dry nitrogen, and finally stored over bright sodium wire.

Solubility Measurements.—These were carried out in an all-glass sealed apparatus by using the technique described by Fairbrother, Scott, and Prophet.[5] For solubilities below room temperature the apparatus was agitated in a methylated spirits–water thermostat, continually cooled by a refrigerator unit, and heated by a conventional heater. An upper limit was set to the range of temperature by the b. p. of the ether and the necessity to ensure that it did not split. In every case, at the end of a completed run a small amount of ether was condensed from the remaining solution, and its infrared absorption spectrum examined. This confirmed the absence of any decomposition.

The ether was pre-treated similarly [5] with the halide under examination. The ampoules containing the saturated ether solution were cracked about the middle without separation and broken under water. After standing for 4—5 hr. the solution was heated to about 90°, cooled, and filtered, and the halide determined volumetrically. The filtered oxide was also ignited and weighed as a check on the halide determination. The latter, however, being capable of a greater precision, was used in calculation of the solubilities. In the Table are given the solubilities (*s*) as g. of halide dissolved by 100 g. of ether, and in Fig. 2 the log mole-fraction of solute (x_1) as a function of $1/T$.

$NbCl_5$		$TaCl_5$		$NbBr_5$		$TaBr_5$		TaI_5	
t	*s*	*t*	*s*	*t*	*s*	*t*	*s*	*t*	*s*
2·6°	10·93	−5·8°	13·24	2·2°	2·99	3·0°	6·41	3·0°	2·29
10·1	12·99	1·8	14·78	5·6	3·20	8·5	7·52	5·8	2·43
15·7	14·99	7·0	15·78	10·0	3·53	18·9	8·80	9·0	2·56
20·0	18·32	16·3	18·39	14·6	3·65	21·4	10·09	15·7	2·94
22·6	23·37	18·5	21·08	17·1	3·73			20·0	3·27
24·9	24·92	20·5	26·61	20·9	4·34				

The accurate computation of the ideal solubilities of these compounds by the formula given by Hildebrand and Scott [6] *viz.*,

$$\log_{10} x_1 = \frac{-\Delta H^\circ_{T(m)}}{4{\cdot}575T(m)}\left(\frac{T(m)}{T} - 1\right) + \frac{\Delta C^\circ_p}{4{\cdot}575}\left(\frac{T(m)}{T} - 1\right) - \frac{\Delta C^\circ_p}{1{\cdot}987}\log_{10}\frac{T(m)}{T}$$

where x_1 is the mole-fraction of solute and $T(m)$ the melting point, is precluded by the absence of any data regarding the change in molar heat capacity on fusion, ΔC°_p. Nevertheless, since this quantity is usually very small in comparison with the molar heat of fusion at the melting point, $\Delta H^\circ_{T(m)}$, a sufficiently approximate value of the ideal solubility can be gained by the use of the first term only. Neglect of the terms in ΔC°_p would not invalidate the present argument. The " ideal " solubilities given in Fig. 2 are calculated on this basis. The values for the melting points and heats of fusion are taken from the work of Alexander and Fairbrother.[3,4]

From Fig. 2 it can be seen that the molar solubilities of niobium and tantalum pentachlorides are almost indistinguishable over the range of temperatures examined. This holds also for the ideal solubilities, in which case the slightly lower heat of fusion of $NbCl_5$ is compensated by its lower melting point.

[4] Alexander and Fairbrother, *J.*, 1949, 2472.
[5] Fairbrother, Scott, and Prophet, *J.*, 1956, 1164.
[6] Hildebrand and Scott, " The Solubility of Non-Electrolytes," New York, 3rd edtn., 1950.

At the higher temperatures the actual solubilities of the pentachlorides and pentabromides are roughly parallel to their ideal solubilities, lying in each case much higher, as would be expected from complex formation. The smaller gradient of the log x_1–$1/T$ curves at lower temperatures is probably due to additional solvation of the complex. This is supported by the evidence of a greater apparent molecular weight at these temperatures as deduced from vapour-pressure measurements. In the case of the bromides, the differences between their actual solubilities and between their ideal solubilities are very close, which again indicates a very similar energy of interaction with ether.

Tantalum pentaiodide, on the other hand, was exceptional (insufficient for the less stable niobium pentaiodide was available for similar experiments); vapour-pressure measurements

FIG. 1.

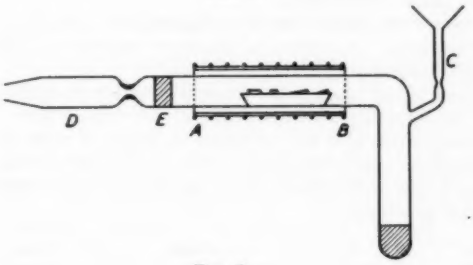


FIG. 3.

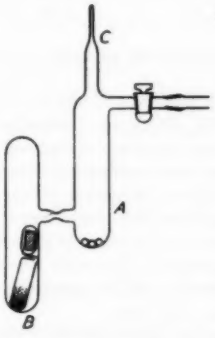
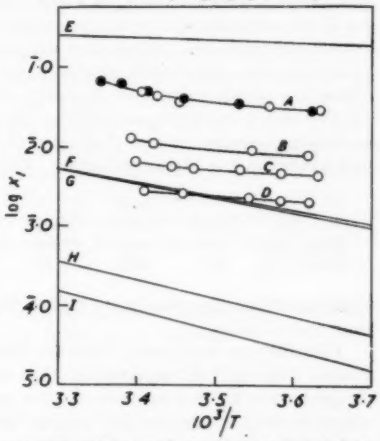


FIG. 2. *Plots of* log x_1 *against* $1/T$.



A, $NbCl_5$ (black circles), $TaCl_5$ (open circles); *B*, $TaBr_5$; *C*, $NbBr_5$; *D*, TaI_5. Curves *E*, *F*, *G*, *H*, and *I* are the ideal solubility curves for TaI_5, $NbCl_5$, $TaCl_5$, $TaBr_5$, and $NbBr_5$ respectively.

gave no evidence of complex formation and the ether could be distilled away, leaving the pentaiodide apparently unchanged. The molar solubility of this halide is much less than of the other four and its solubility lies well below the ideal. As regards the actual position of the ideal solubility curve, this is calculated with the use of the rather low heat of fusion (1·6 kcal./mole) derived as a difference between the relatively much larger heats of sublimation (19·7 kcal./mole) and of volatilisation (18·1 kcal./mole). Any errors in the magnitude of the heat of fusion, however, would be unlikely to affect qualitatively the present conclusion. We were also unable to observe any Friedel–Crafts-type catalytic activity of tantalum pentaiodide. This lack of acceptor properties in tantalum pentaiodide is probably due to the greater screening of the metal acceptor atom by the large iodine atoms. The pentafluorides are excellent Friedel–Crafts catalysts.[1]

Vapour-pressure Measurements.—These were carried out in a conventional type of apparatus in which a measured amount of dry ether contained in a 25 c.c. graduated pipette was condensed by cooling on a weighed quantity of halide contained in a 100 c.c. conical reaction flask. The halide was introduced under nitrogen in a sealed ampoule, cracked about its middle and broken, by shaking, under the ether. The reaction flask contained also a quantity of dry glass wool to assist in the attainment of equilibrium. It was attached to the rest of the apparatus by a flexible glass spiral and continuously shaken mechanically under the surface of the thermostat

water. Ingress of moisture through the joint (B24) of the removable reaction vessel was prevented by a thick layer of Apiezon-Q compound covered in turn by a layer of collodion. In each system, measurements were made at the temperature of melting ice and at about 16° (±0·02°). The thermostat could be lowered from the reaction vessel, and the entire measuring system was enclosed in a large air thermostat kept at 19—20° ± 0·5°, the manometers being read from a distance by a cathetometer. The measuring system also included an additional bulb into which pure ether was condensed which, with its associated manometer, permitted readings to be made of the depression of vapour pressure.

Portions of the ether were removed from the reaction system from time to time by cooling the pipette, which was then returned to 20° for measurement, due allowance being made for the ether present in the " dead space " of the apparatus.

Even with the aid of the glass wool and with continuous agitation, equilibrium was sometimes established very slowly, especially when solid phase was present.

At the conclusion of a run the reaction vessel was filled with dry nitrogen, and samples of the complex were removed, in a dry box, for analysis. A number of specimens for analysis and for *X*-ray examination were also prepared independently as described below.

All the pressure–composition diagrams were of the usual type, showing a rather ill-defined break which corresponded approximately to the solubility measurements, a very sharp " knee " where the pressure dropped abruptly, at a composition of 1 mol. of halide to 1 mol. of ether, to the low dissociation pressure of the ether complex. The complexes were so stable and the dissociation pressures so low that in most cases it was very difficult to pump off any more ether and condense it in liquid nitrogen. These were as follows:

Complex	Temp.	Press. (mm.)	Temp.	Press. (mm.)	Complex	Temp.	Press. (mm.)	Temp.	Press. (mm.)
$NbCl_5,Et_2O$	0°	0·39	16·69°	0·73	$NbBr_5,Et_2O$	0°	2·06	15·89°	3·21
$TaCl_5,Et_2O$	0	0·92	15·92	1·96	$TaBr_5,Et_2O$	0	6·32	15·90	9·63

Each tantalum complex has a higher dissociation pressure than the niobium, and each bromide than the chloride.

Calculations were made, from the lowering of the vapour pressure in dilute solution, by use of Raoult's law and the assumption that the complex was MX_5,Et_2O, *i.e.*, virtually increasing the concentration by this amount of ether complexed. No great accuracy is claimed for the results, which showed a considerable scatter, but the mean values were sufficiently close to show that at 16° MX_5,Et_2O was essentially the species present in solution but that at 0° the solutions were effectively more concentrated, a result of the further solvation of the complexes.

System Niobium Pentachloride–Diethyl Ether.—Niobium pentachloride dissolved readily to give a yellow solution, which deposited green-yellow crystals of the *ether complex*, m. p. 83° (decomp.) [Found: Nb, 27·3, 27·1, 27·2; Cl, 51·2, 51·1, 51·2%; *M*, in solution at 0°, 1096; at 16·7°, 354. $NbCl_5,(C_2H_5)_2O$ requires Nb, 27·0; Cl, 51·5%; *M*, 355].

System Tantalum Pentachloride–Diethyl Ether.—Tantalum pentachloride dissolved readily to give a colourless solution which deposited colourless crystals of the *ether complex*, m. p. 80° (decomp.) [Found: Ta, 41·4, 42·5, 42·1; Cl, 40·1, 40·8, 40·8%; *M*, in solution at 0°, 680; at 15·9°, 422. $TaCl_5,(C_2H_5)_2O$ requires Ta, 41·9; Cl, 41·0%; *M*, 444].

System Niobium Pentabromide–Diethyl Ether.—Niobium pentabromide dissolved to give a red solution which deposited brown crystals of the *ether complex*, m. p. 71° (decomp.) [Found: Nb, 17·3, 17·5, 17·7, 16·3, 16·8, 16·6; Br, 70·0, 69·4, 69·0, 62·1, 61·9, 63·6%; *M*, in solution at 0°, 854; at 15·9°, 594. $NbBr_5,(C_2H_5)_2O$ requires Nb, 16·4; Br, 70·5%; *M*, 567].

System Tantalum Pentabromide–Diethyl Ether.—Tantalum pentabromide dissolved to give an orange-coloured solution which deposited orange crystals of the *ether complex*, m. p. 77° (decomp.) [Found: Ta, 27·5, 27·8, 27·9, 28·1, 27·9, 27·9; Br, 59·6, 61·2, 59·8, 60·2, 58·6, 59·0%; *M*, in solution, at 0°, 854; at 15·9°, 675. $TaBr_5,(C_2H_5)_2O$ requires Ta, 27·6; Br, 61·0%; *M*, 655].

X-Ray Examination.—Samples of the ether complexes for this purpose and for analysis were prepared in the apparatus shown in Fig. 3 in which *C* is a thin-walled Pyrex glass capillary. The halide *B* and dry ether were successively sublimed into *A*. After the reaction and removal by pumping of excess of ether, the crystals of the complex were ground by shaking with glass balls on a vibro-shaker. The apparatus was then inverted, and the etherate shaken into the capillary. The apparatus was then filled with dry nitrogen, and the capillary broken off and quickly sealed with soft wax.

XUM

Diffraction photographs were taken with Cu-K_α radiation by use of a nickel filter and a 19 cm. camera. The *X*-ray photographs were very complex and many-lined. Photographs of the pure halides were also taken for comparison.

The two chlorides and the two bromides all showed similar *X*-ray patterns: with a given halogen the spacings were almost indistinguishable. On the other hand, although the ether complexes of the two pentachlorides are isomorphous, those of the two pentabromides appear to differ from one another and from those of the pentachlorides.

Pyrolysis of the Ether Complexes.—This was investigated primarily as a possible route to the preparation of the oxyhalides, though this proved not to be the best method of preparing them. The ether complexes were heated in a vacuum for varying periods at several temperatures up to about 500°. The volatile products were condensed at −195°, and both they and the involatile residues analysed. The results indicated that the essential stages in the decomposition were

$$MHal_5,Et_2O \longrightarrow MOHal_3 + 2EtHal;\ MOHal_3 \longrightarrow MHal_5 + M_2O_5$$

The composition of the solid products varied according to the temperature and time of heating, but in general, heating at about 100° led to a solid product, which was analysed as the oxytrihalide. Heating at higher temperatures gave products which varied according to the halide under examination. Ether complexes of niobium pentachloride and pentabromide at 90° and 112°, respectively, gave oxytrihalides. These, on further heating *in vacuo* at 200° and 250°, sublimed very slowly without decomposition, giving very fine crystals (diffuse *X*-ray pattern), but disproportionated at still higher temperatures. The tantalum halide complexes, however, showed a marked disproportionation of the oxytrihalides below 300°. After the tantalum pentachloride complex had been heated at 490° for 16 hr. and the pentabromide complex at 450° for 6 hr., almost all the halogen was eliminated, with a sublimate which was found to be the pentahalide, and a residue which *X*-ray diffraction showed to be the pentoxide. In all cases ethyl halide was eliminated as a volatile product.

We are indebted to Mr. J. F. Nixon for assistance with the solubility measurements and to Messrs. Imperial Chemical Industries Limited for the loan of the *X*-ray camera.

THE UNIVERSITY, MANCHESTER, 13. [*Received, March 19th*, 1958.]

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636. *The Infrared Spectra of Some Simple and Complex Carbonates.*

By B. M. GATEHOUSE, S. E. LIVINGSTONE, and R. S. NYHOLM.

The infrared spectra of some carbonato-metal complexes have been examined in the region between 4000 and 700 cm.$^{-1}$. The spectra have been compared with those of simple, acid, basic, and organic carbonates, and characteristic frequencies have been assigned for these compounds. Strong absorption bands, which are absent in the spectra of ionic carbonates, occur at 1577—1493, 1338—1272, and 1080—1020 cm.$^{-1}$ in those of the carbonato-complexes. The diagram below summarises the spectra.

The infrared spectra of dimethyl, diethyl, and diphenyl carbonate have also been recorded.

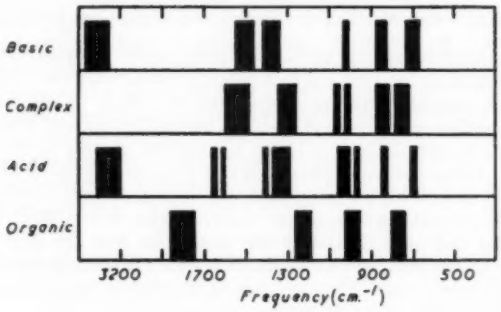
EARLIER [1] we reported the infrared absorption spectra of some nitrato-metal complexes and assigned the bands corresponding to the vibrations ν_1, ν_2, ν_4, and ν_6 of the covalently bound nitrate group. In this investigation a number of carbonato-metal complexes have been examined in order to ascertain whether their spectra are related to the simple carbonates, in the same way as the spectra of nitrato-complexes are related to those of ionic nitrates, since the carbonate and nitrate ions are both planar XY_3 groups possessing D_{3h} symmetry.

The spectra of simple ionic carbonates fall generally into one of two groups according

[1] Gatehouse, Livingstone, and Nyholm, *J.*, 1957, 4222.

to whether the compound is of the calcite or aragonite type. These compounds have been extensively examined [2,3,4,5] and the differences between the two groups arise mainly from intermolecular coupling of the out-of-plane bending mode (ν_2) and the lower symmetry in the crystal.[6]

Nakamoto *et al.*[7] recently reported the infrared absorption spectra of three carbonato-complexes of tervalent cobalt and made assignments with reference to the carbonate ion. They showed that co-ordination by the carbonato-group causes the appearance of a band which is inactive for the carbonate ion, and the splitting of the degenerate mode ν_3, owing to the lowering of symmetry of the ligand, as we demonstrated for the nitrato-complexes. Duval *et al.*[8] had earlier examined some carbonato-complexes of bi- and ter-valent cobalt



and of bivalent copper, observing the appearance of a new absorption band, ν_2, in the vicinity of 1050 cm.$^{-1}$. However, these workers apparently did not resolve a broad absorption band in the region 1300—1500 cm.$^{-1}$.

Miller and Wilkins [2] reported the spectra of three hydrogen carbonates (NH_4^+, Na^+, and K^+) which are very similar to those of the complex carbonates and show the loss of degeneracy of ν_3, which results in the appearance of bands in the regions 1660—1620 (ν_4) and 1410—1295 cm.$^{-1}$ (ν_1).

The spectra of a number of basic carbonates have also been reported,[2,4] which show similarities to those of the complex carbonates. Apparently hydrogen bonding in these compounds causes a lowering of symmetry of the carbonato-group from D_{3h} to C_{2v}.

In addition to the carbonato-complexes we have examined three organic carbonates and the spectra of these are compared with the carbonates mentioned above.

Experimental

Absorption Measurements.—The infrared spectra were obtained with a Grubb-Parsons double-beam infrared spectrometer, equipped with an S3A monochromator and a rock-salt prism. The samples were ground in an agate vibration mill. The mulling agents used were Nujol, and hexachlorobutadiene for the region (6—8 μ) obscured by Nujol absorption bands. The samples were examined between rock-salt plates, coated with polystyrene, as described by one of us,[9] to ensure that there would be no replacement of the carbonato-group by chloride from the rock-salt plates.

Preparation of Compounds.—Sodium carbonatocuprate(II) *trihydrate.* This compound was

[2] Miller and Wilkins, *Analyt. Chem.*, 1952, **24**, 1253.
[3] Loisfert and Pobeguin, *Compt. rend.*, 1952, **235**, 287.
[4] Hunt, Wisherd, and Bonham, *Analyt. Chem.*, 1950, **22**, 1478.
[5] Couture, *Ann. Phys.*, 1947, **2**, 5.
[6] Decius, *J. Chem. Phys.*, 1954, **22**, 1946; 1955, **23**, 1290.
[7] Nakamoto, Fujita, Tanaka, and Kobayashi, *J. Amer. Chem. Soc.*, 1957, **79**, 4904.
[8] Duval, Duval, and Lecomte, *Bull. Soc. chim. France*, 1943, **10**, 517.
[9] Gatehouse, *Chem. and Ind.*, 1957, 1351.

prepared by Applebey and Lane's method [10] (Found: Cu, 22·1; CO_3^{2-}, 42·6. Calc. for $C_2H_6O_9CuNa_2$: Cu, 22·4; CO_3^{2-}, 42·4%).

Potassium carbonatocobaltate(II) *tetrahydrate.* This was made similarly (Found: Co, 17·3; CO_3^{2-}, 36·1. Calc. for $C_2H_8O_{16}CoK_2$: Co, 17·9; CO_3^{2-}, 36·4%).

Potassium carbonatocobaltate(III) *trihydrate.* The method described by Mori *et al.*[11] was used (Found: Co, 16·0; CO_3^{2-}, 44·4. Calc. for $C_2H_6O_{12}CoK_3$: Co, 14·4; CO_3^{2-}, 43·9%). It seems impossible to obtain this compound quite pure, as seen from the analyses by Mori *et al.*[11] We prepared it a number of times and in each case the infrared absorption spectra were identical.

Hexamminocobalt(III) *carbonatocobaltate*(III). The method of preparation used was that of Mori *et al.*,[11] being more straightforward than that of McCutcheon and Schuele.[12] The product was dried *in vacuo* over phosphoric oxide (Found: Co, 29·6. Calc. for $C_3H_{18}O_9N_6Co_2$: Co, 29·5%).

Carbonatopentamminocobalt(III) *chloride.* The compound was prepared as described by Gmelin [13] (Found: Co, 24·8; Cl, 14·5. Calc. for $CH_{15}O_3N_5ClCo$: Co, 24·6; Cl, 14·8%).

Carbonatotetramminocobalt(III) *sulphate trihydrate.* The method quoted by Gmelin [14] was used (Found: Co, 22·9. Calc. for $C_2H_{30}O_{13}N_6SCo_2$: Co, 22·5%).

Carbonatobisethylenediaminecobalt(III) *chloride.* An aqueous solution of *trans*-dichlorobisethylenediaminecobalt(III) chloride was treated with the calculated quantity of sodium carbonate as described by Gmelin.[15] The carbonato-complex was dried at 100° (Found: Cl, 12·6. Calc. for $C_5H_{16}O_3N_4ClCo$: Cl, 12·9%).

Carbonatobisethylenediaminecobalt(III) *bromide.* The bromide was prepared in an analogous manner to the chloride from *trans*-dibromobisethylenediaminecobalt(III) bromide (Found: Br, 24·8. Calc. for $C_5H_{16}O_3N_4BrCo$: Br, 25·0%).

Carbonatobisethylenediaminecobalt(III) *iodide.* The iodide was prepared by treating a warm aqueous solution of the chloride with potassium iodide. On cooling, the solution deposited crystals of the iodide (Found: I, 34·1. Calc. for $C_5H_{16}O_3N_4ICo$: I, 34·6%).

Organic Carbonates.—The purity of the organic carbonates was checked by the measurement of the refractive index for the dimethyl and the diethyl ester and by a m. p. determination for the phenyl ester. The former were examined in the liquid state between rock-salt plates and the latter in the solid state in Nujol and hexachlorobutadiene mull.

Attempted Preparation of the Double Carbonate of Potassium and Nickel.—Attempts were made to prepare the double carbonate of potassium and nickel, reported by Deville.[16] The method used for the preparation of the copper and cobaltous complexes, described above, was tried, as well as Deville's method. Crystalline products were obtained with both procedures, but analysis showed that the products did not have the composition, $K_2CO_3,NiCO_3,4H_2O$, reported by Deville.

Results and Discussion

The carbonate ion has D_{3h} symmetry, giving rise to four vibrations,[17] which are listed in Table 1. The absorption spectra of some alkali, alkaline-earth, and heavy-metal

Table 1. *Fundamental frequencies of the carbonate ion.*[17]

Type [18]	Raman *	Infrared *	CO_3 [11]	cm.$^{-1}$	Assignment
A_1'	a	ia	ν_1	1063	C–O sym. stretching
A_2''	ia	a	ν_2	879	CO_3 out-of-plane deformation
E'	a	a	ν_3	1415	C–O asymm. stretching
E'	a	a	ν_4	680	in-plane deformation (or rocking)

* a = active; ia = inactive.

carbonates, reported by Miller and Wilkins,[2] display only two strong bands, at 1450—1410 and 880—840 cm.$^{-1}$ with, in some cases, a weak band at 715—685 cm.$^{-1}$. The

[10] Applebey and Lane, *J.*, 1918, **113**, 610.
[11] Mori, Shibata, Kyuono, and Adachi, *Bull. Chem. Soc. Japan*, 1956, **29**, 883.
[12] McCutcheon and Schuele, *J. Amer. Chem. Soc.*, 1953, **75**, 1845.
[13] Gmelin, "Handbuch der anorganische Chemie," Verlag Chemie, Berlin, 1930, **58**, *B*, 199.
[14] *Op. cit.*, p. 281.
[15] *Op. cit.*, p. 283.
[16] Deville, *Ann. Chim. Phys.*, 1851, **33**, 75.
[17] Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," van Nostrand, New York, 1945, p. 178.
[18] Meister, Cleveland, and Murray, Research Publications, Illinois Institute of Technology, Vol. 6, No. 1, Jan. 1948.

vibration, ν_1, gives rise to an absorption band only in simple carbonates of the aragonite type.

We have examined barium carbonate and found that it gives three strong absorption bands, 1420, 857, and 692 cm.$^{-1}$. Barium carbonate, containing ^{13}C was also examined,[19] and it was found that the band at 857 cm.$^{-1}$ is shifted to 832 cm.$^{-1}$, whereas the other bands are shifted only by a few cm.$^{-1}$. This identifies the band in the region of 850 cm.$^{-1}$ as the out-of-plane rocking vibration, ν_2, of the carbonate ion.

When the carbonate ion is covalently bound through one oxygen atom the symmetry is lowered and the carbonato-group belongs to the point group C_{2v}. If the carbonato-group is bidentate the symmetry is the same as of the monodentate ligand. Table 2 lists the vibration types and assignments of the carbonato-ligand.

TABLE 2. *Fundamental frequencies of the covalently bound carbonato-group.*

Type [18]	Raman	Infrared	Carbonato frequency	Assignment
A_1	a	a	ν_2	CO_2 bending
A_1	a	a	ν_1	CO_2 sym. stretch.
A_1	a	a	ν_3	CO stretch.
B_2	a	a	ν_6	Non-planar rock.
B_1	a	a	ν_4	Asym. stretch.
B_1	a	a	ν_5	Planar rock.

The principal absorption bands of the carbonato-complexes, examined in this investigation, are given in Table 3. By reference to the spectra of $[Co(NH_3)_6]Cl_3$ and *cis*-$[Co\ en_2Cl_2]Cl$, the bands due to co-ordinated ammonia and ethylenediamine have been identified in the spectra of the appropriate carbonato-complexes and are omitted in Table 3.

The vibration, ν_3, of the carbonate ion (see Table 1), being doubly degenerate, is split into two components when the carbonate ion is co-ordinated; these are now designated ν_4 and ν_1. A similar splitting occurs with basic, acid, and organic carbonates. The frequency ranges for these compounds are given in Table 5. The differences between the results reported here for $[Co(NH_3)_5CO_3]^+$ and those of Nakamoto *et al.*[7] could have arisen from

TABLE 3. *Infrared absorption bands of carbonato-complexes (cm.$^{-1}$).*

	ν_4	ν_1	ν_3	ν_6	ν_2 or ν_5
$Na_2[Cu(CO_3)_2].3H_2O$	1529 s	1326 s	1066 m 1050 m	850 s	755 s
$K_2[Co(CO_3)_2].4H_2O$	—	1338 m	1082 m 1049 m	884 m	799 s 766 m
$K_3[Co(CO_3)_3].3H_2O$	1527 s	1330 s	1080 w 1037 m	851 m	809 m
$[Co(NH_3)_6][Co(CO_3)_3]$	1523 s	1285 s	1073 w 1031 w	889 w	738 m
$[Co(NH_3)_5CO_3]Cl$	1493 s	1297 s	1057 m 1043 m	873 s 848 s	738 m
$[Co(NH_3)_4CO_3]_2SO_4.3H_2O$	*	1260 s	— 1021 m	856 w	756 m
$[Co\ en_2CO_3]Cl$	1577 s	1281 s 1272 s	1059 w 1035 w	830 s	754 m
$[Co\ en_2CO_3]Br$	1575 vs	1282 s 1276 s	1059 s 1038 s	825 s	757 s
$[Co\ en_2CO_3]I$	1565 m	1290 v.w.sh. 1278 s	1055 m 1034 m	824 s	756 m

w = weak; m = medium; s = strong; vs = very strong; sh = shoulder; en = ethylenediamine.

* Band here is obscured by NH_3 and H_2O bands in region 1640—1550 cm.$^{-1}$.

confusion over ammonia and water absorption bands which occur in the same regions as ν_4 for the carbonate ligand or could have been due to the KBr disc technique used by the latter workers.

The hydrogen carbonates show a further splitting of ν_3 and ν_1, the bands being well

[19] Comyns and Gatehouse, unpublished work.

defined. This effect probably arises from interaction between neighbouring HCO_3 groups. Zachariasen [20] described the crystal lattice of sodium hydrogen carbonate wherein two oxygens of each HCO_3 group are hydrogen-bonded to neighbouring HCO_3 groups and the third oxygen is "free." It is not unreasonable to expect a higher bond order for the "free" C–O bond, with which the appearance of an absorption in the 1660—1620 cm.$^{-1}$ region is consistent.

TABLE 4. *Infrared absorption bands of some organic carbonates.*

	ν_4 (cm.$^{-1}$)	ν_1	ν_6	Other bands ascribed to the carbonato-group	
Dimethyl carbonate	1760 s	1280 s	793 s	969 s	914 s
Diethyl carbonate	1750 s	1262 s	790 s	1021 s	858 s
Diphenyl carbonate [b]	1779 s	1260 s	790 s	1021 m	912 w, 874 w
Methyl phenyl carbonate [22]	1755 s	1262 s	a	a	
Ethyl phenyl carbonate [22]	1757 s	1252 s	a	a	
Ethylene carbonate (liquid) [23]	1870 s	1162 s	774 m	1074 s	974 s
(solid)	1810 s	1163 s	774 s	1078 s	972 s

[a] No bands are reported below 1060 cm.$^{-1}$. [b] The following bands were also obtained for diphenyl carbonate: 1599 m, 1500 s, 1188 s, 1162 s, 1073 m, 955 m, 764 m, 749 s, 712 w, 686 s.

The spectra of some organic carbonates are listed in Table 4 and are similar to the spectra of the complex carbonates. The absorption bands ν_4 and ν_1 occur in the ranges 1870—1750 and 1280—1162 cm.$^{-1}$ respectively. This greater difference in frequency between ν_4 and ν_1 is to be expected if we assume less ionic character in the organic carbonates than in the carbonato-complexes. The frequency of ν_4 in the organic carbonates corresponds to the C=O frequency found in a large number of carbonyl compounds.[21]

TABLE 5. *Frequency ranges of carbonate absorption bands (cm.$^{-1}$).*

Type of carbonate	ν_3		ν_1	ν_2		ν_4
Simple	1470—1420		1090—1020 w [*]	890—820		750—680
	OH	ν_4	ν_1	ν_2	ν_6	ν_3 or ν_5
Basic [2, 4]	3390—3270	1515—1470	1425—1325	1049—1047	877—835	712—686
Complex	—	1577—1493	1338—1260	1082—1055 1050—1021	889—824	809—738
Acid [2]	3300—3200	1660—1655 1630—1620	1410—1400 1370—1295	1050—1010 1000—990	840—830	705—698
Organic [22, 23]	—	1870—1750	1280—1252	1021—969(?)	793—774	—

[*] See p. 3140.

The normally forbidden absorption, ν_1, which appears weakly only in simple carbonates of the aragonite type, is active for the co-ordinated group (ν_2) and appears with medium intensity. This band is well defined only in the compounds not containing ethylenediamine, as the latter has a strong sharp band at 1053 cm.$^{-1}$, the carbonato-bands appearing on either side. It can be seen from Table 3 that there is little variation in ν_2 for the complexes, although the trend is similar to that observed for the nitrato-group,[1] with the more covalent compounds having the lower frequencies. A splitting of ν_2 is observed in the hydrogen carbonates and in the carbonato-complexes, and probably arises out of interaction of neighbouring groups; the possibility of its arising from Fermi resonance of ν_2 with $2\nu_5$ (or $2\nu_3$) where ν_5 (or ν_3) occurs at approximately 520—540 cm.$^{-1}$, must not be overlooked.*

The out-of-plane vibration, designated ν_2 for simple carbonates, becomes ν_6 for the carbonato-group, and apart from the organic carbonates does not differ greatly in frequency

* The authors are grateful to the referees for this suggestion.

[20] Zachariasen, *J. Chem. Phys.*, 1933, **1**, 634.
[21] Hartwell, Richards, and Thompson, *J.*, 1948, 1436.
[22] Hales, Jones, and Kynaston, *J.*, 1957, 618.
[23] Angel, *Trans. Faraday Soc.*, 1956, **52**, 1178.

from that in the simple carbonates. The differences in this region between the calcite and aragonite type carbonates are discussed in detail by Decius.[6]

The carbonate-ion absorption ν_4 is doubly degenerate, giving rise to ν_3 and ν_5 for the complex carbonates. However, only one absorption band is observed below 800 cm.$^{-1}$ and its assignment would not be certain until the KBr region was examined.

The spectra are summarised in the diagram.

The authors thank Dr. D. J. Millen for helpful advice, Professor J. V. Quagliano for reading the manuscript, and Dr. M. L. Tobe for supplying a sample of carbonatotetramminocobalt(III) sulphate. One of them (B. M. G.) gratefully acknowledges a grant from the United Kingdom Atomic Energy Authority.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1. [*Received, April 16th*, 1958.]

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637. *The Ultraviolet Absorption Spectrum of Dinitrogen Tetroxide in Organic Solvents.*

By C. C. ADDISON and J. C. SHELDON.

The ultraviolet absorption spectrum of dinitrogen tetroxide in *n*- or *cyclo*hexane closely resembles the spectrum of the vapour ($\lambda_{max.}$ 343 mμ; ε 233) with no evidence of fine structure. In non-aromatic solvents (*n*- or *cyclo*hexane, carbon tetrachloride, 1 : 4-dioxan, diethyl ether, chloroform, acetic acid, ethyl acetate, acetic anhydride, methyl cyanide) the extinction coefficient decreases in a regular manner with increase in dipole moment of the solvent, whereas decrease in $\lambda_{max.}$ is determined largely by donor properties of the solvent. The results suggest that in mixtures of dinitrogen tetroxide with donor solvents, discrete molecules of addition complex are not present, but that partial electron-transfer occurs. In aromatic (π-donor) solvents (benzene, toluene, *p*-xylene, chlorobenzene) $\lambda_{max.}$ is unchanged, but the ε values now increase with π-donor strength, confirming that the type of electronic interaction in π- and 'onium donor solvents is different. The contribution of nitrogen dioxide to absorption by dinitrogen tetroxide is discussed.

IT has been shown in previous papers that the chemical reactivity of liquid dinitrogen tetroxide is considerably modified in the presence of electron-donor solvents. Addition compounds are formed in the solid state,[1] and vapour-pressure studies give evidence of pronounced interaction between the tetroxide and organic donor molecules (Don) in the liquid state also.[2] Reactions of the mixtures with metals are most readily interpreted on the assumption that ionic species $(Don)_n{\cdot}NO^+$ and NO_3^- are present,[3] but the conductivity of the solutions is not high and it is unlikely that this is the form in which most of the molecules are present. The negative deviations of vapour pressure which occur with strong donor solvents such as ethyl acetate [2] indicate that in equimolar mixtures approximately half the molecules present form addition compounds. An alternative view is that partial charge-transfer from each solvent to each tetroxide molecule occurs. The ultraviolet absorption spectra of mixtures has therefore been examined; if a high proportion of the tetroxide molecules present form ionic species or discrete molecules of addition compound, then pronounced changes in the form of the spectrum are to be expected, whereas partial charge-transfer may not modify the spectrum to the same extent. The spectrum of dinitrogen tetroxide in the vapour phase has been well characterised over

[1] Addison and Sheldon, *J.*, 1956, 1941, 2705, 2709.
[2] *Idem*, *J.*, 1957, 1937.
[3] Addison, Sheldon, and Hodge, *J.*, 1956, 3900.

the 240—500 mμ range by Hall and Blacet,[4] who resolved the spectrum of the gaseous N_2O_4–NO_2 mixture at 25° by obtaining the absorption at several vapour pressures, and employing a mechanical analogue differential analyser.

Results and Discussion

Spectrum of N_2O_4 *in* n- *or* cyclo-*Hexane.*—These solvents show inert solvent behaviour so far as vapour pressures are concerned.[2] Because of the absorption density of the tetroxide at the wavelengths used, approximately centimolar solutions were employed The spectrum is shown in Fig. 1. Identical results were obtained in *n*- or *cyclo*-hexane provided that solvent absorption was negligible (*cyclo*-hexane was not used at wavelengths shorter than 260 mμ). The spectrum in hexane is very similar to that in the vapour; significant details of each spectrum are given in Table 1.

The general agreement in the two phases confirms the view that saturated hydrocarbons are inert with respect to dinitrogen tetroxide. The ε values for the solution show some increase over the vapour values, and the 340 mμ maximum undergoes a very slight red shift. Bayliss and McRae [5] suggest that all solutes should suffer a red shift in the spectrum on passing from vapour to solution, though solvation may mask this with a greater blue shift. Although changes in ε cannot be predicted, it is apparent from their data that ε increases for many substances from vapour to liquid phase. In view of the general agreement shown in Table 1, there is interest in Whittaker's observation [6] that the optical absorption coefficient of nitrogen dioxide is the same in both the liquid and the gas phase.

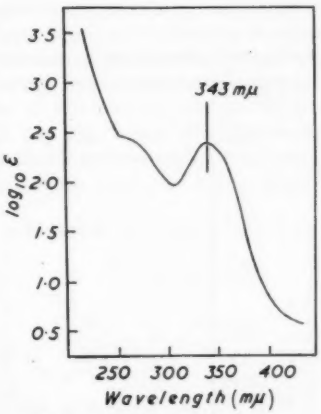


Fig. 1. *Spectrum of* N_2O_4 *in* n- *or* cyclo-*hexane.*

There is a complete absence of fine structure in the spectrum in both phases; reasons for this with respect to the gas phase have been discussed.[4] The small absorption by hexane solutions at 400 mμ (at which wavelength absorption by tetroxide in the vapour is zero) arises from the presence of small quantities of nitrogen dioxide unavoidably present in the solutions. The contribution of nitrogen dioxide to absorption by the tetroxide solutions is discussed later.

Table 1.

	Hexane solution (18°)		Vapour phase (25°)	
	λ (mμ)	ε	λ (mμ)	ε
Inflexion	270	240	260	210
Minimum	308	96	306	112
Maximum	343	233	340	179
	400	8	400	0

* Deduced from the results of Hall and Blacet, on the assumption that tetroxide vapour behaves as an ideal gas.

Interpretation of the Tetroxide Spectrum.—Possible assignment of the bands in the spectrum can be made on the basis of resemblances between the carbonyl and the nitro-group, to which attention has been drawn by Bayliss and McRae.[5] Similar weak absorption bands at 280 mμ are observed with each group (cf. acetone, $\lambda_{max.}$ 279, ε 13 in heptane;

[4] Hall and Blacet, *J. Chem. Phys.*, 1952, **20**, 1745.
[5] Bayliss and McRae, *J. Phys. Chem.*, 1954, **58**, 1002, 1006.
[6] Whittaker, *J. Chem. Phys.*, 1956, **24**, 780; Steese and Whittaker, *ibid.*, p. 776.

nitromethane, $\lambda_{max.}$ 278, ε 18 in heptane). McMurry [7] has suggested that in the carbonyl group this bond is due to excitation of an electron of the oxygen lone pair to an anti-bonding π-orbital of the C–O bond. This is a forbidden transition, thus ε is small. The nitro-group is probably capable of a similar transition, a non-bonding electron from the oxygen atoms passing to the lowest vacant π-orbital of the group. The submerged maximum (*i.e.*, inflexion) in the absorption curve at about 270 mμ might reasonably be assigned to this transition. αβ-Dicarbonyl compounds possess two weak absorption maxima, one near 280 mμ and one at longer wavelength (*e.g.*, diacetyl, 286 and 416 mμ). This is interpreted [7] in terms of the conjugated π-orbitals of the two carbonyl groups, the antibonding π-orbitals of the isolated groups being replaced by two different antibonding π-orbitals in the conjugated system. The two bands are then due to excitation of the oxygen lone-pair electron to one or other of these orbitals. A band at 340 mμ is not a general property of a single nitro-group, and from the analogy with conjugated diketones the second absorption maximum for dinitrogen tetroxide at 340 mμ may be the result of conjugation of the two nitro-groups. In this connexion it is relevant that these two groups

FIG. 2.

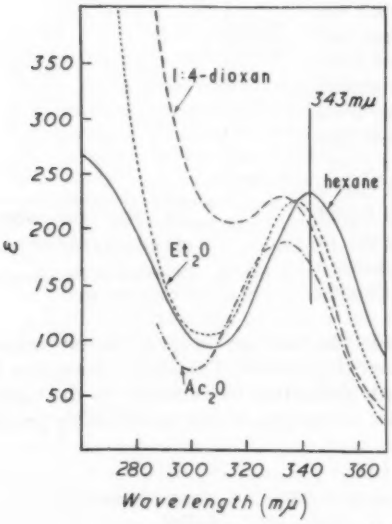
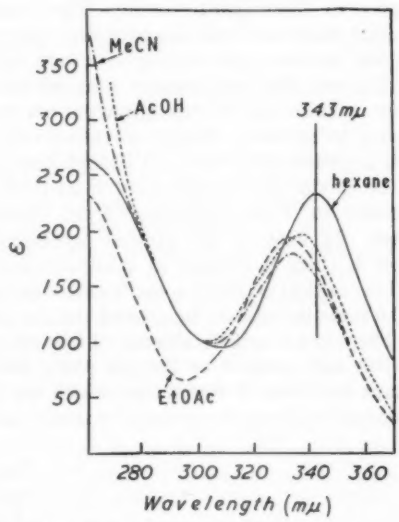


FIG. 3.



FIGS. 2 and 3. *Spectrum of N_2O_4 in various non-aromatic solvents.*

do not rotate with respect to one another.[8] The fact that the wavelength separation of the two tetroxide bands is smaller than for diacetyl would then indicate that conjugation between the two nitro-groups is less pronounced.

Absorption Spectra in Other Aliphatic Solvents.—Though the spectrum of the tetroxide in *n*-hexane could be studied down to 220 mμ, it was not usually possible to measure the spectrum in other solvents below about 280 mμ. The 343 mμ band could still be characterised with all the solvents employed; $\lambda_{max.}$ and ε values for this band in aliphatic solvents are shown in Table 2 in order of dipole moment, and the spectra are shown in Figs. 2 and 3.

The C–Cl bond in carbon tetrachloride has dipolar character and, in spite of the resultant zero dipole moment of the molecule, dipole interaction with dinitrogen tetroxide was apparent

[7] McMurry, *J. Chem. Phys.*, 1941, **9**, 231, 241.
[8] Giauque and Kemp, *ibid.*, 1938, **6**, 40; Chalvet and Daudel, *J. Chim. phys.*, 1952, **49**, 77.

in vapour-pressure measurements.[2] However, the absorption of dinitrogen tetroxide in carbon tetrachloride was found to be identical with that in hexane (Fig. 4), so that it is the permanent dipole of the solvent which is significant in considering modifications of the

TABLE 2.

Solvent	Dipole moment of solvent	$\lambda_{max.}$ (mμ)	ε	Solvent	Dipole moment of solvent	$\lambda_{max.}$ (mμ)	ε
n-Hexane	0	343	233	* Acetic acid	1·75	336	197
Carbon tetrachloride	0	343	233	* Ethyl acetate	1·81	333	195
* 1 : 4-Dioxan	0·45	332	230	* Acetic anhydride ...	2·8	333	190
* Diethyl ether	1·15	337	225	* Methyl cyanide	3·37	333	177
Chloroform	1·15	342	200				

* Donor solvents with respect to dinitrogen tetroxide.

spectrum. The non-donor chloroform molecule has a permanent dipole, and interaction with the tetroxide is revealed clearly in a variation in ε, though not in wavelength.

The data in Table 2 indicate that the donor properties of the solvent, and its dipole moment, influence the spectrum in different ways which can be clearly distinguished. Thus, the ε value decreases regularly with increase in the dipole moment of the solvent, irrespective of whether the solvent possesses donor properties. On the other hand, decrease in $\lambda_{max.}$ is determined largely by the donor properties of the solvent. The position of acetic acid in Table 2 has special interest. In phase studies,[1] and vapour-pressure studies,[2] where solutions of acetic acid in dinitrogen tetroxide were involved, the acid fell into place in the list of solvents when it was assumed to exist as the dimer and the corresponding dipole moment (0·83) employed. In the solutions used for spectra the position is reversed. Acetic acid becomes the solvent; it shows anomalous behaviour if regarded as dimeric, but falls into place with other donor solvents if the dipole moment of the monomer (1·75) is regarded as operative.

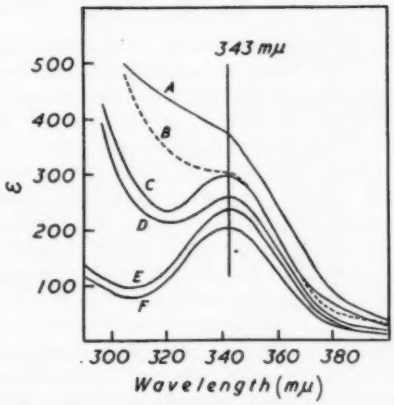


FIG. 4. *Spectrum of* N_2O_4 *in aromatic solvents*: (*A*) p-*xylene*, (*B*) *toluene*, (*C*) *benzene*, (*D*) *chlorobenzene*; *also* (*E*) *carbon tetrachloride or* n- *or* cyclo-*hexane and* (*F*) *chloroform*.

Since the wavelength shift occurs only with donor solvents, it is clearly due to partial electron-donation and not dipole interaction. The electrons from the organic donor may be regarded as entering the lowest vacant orbital of the tetroxide, and it is to this orbital that electrons are excited by ultraviolet absorption by the tetroxide at 343 mμ. The weakly donated electrons are easily expelled from the tetroxide π-orbital by the excitation process, the extra energy required appearing as a decrease in $\lambda_{max.}$. This decrease (10 mμ) is equivalent to a change in the excitation energy of about 2 kcal. $mole^{-1}$, which is of the same order as the energy of interaction determined from heats of mixing. This apparently small solvent–tetroxide interaction is nevertheless sufficient to alter markedly the nature as well as the degree of chemical reactivity of the tetroxide with change of solvent.

The general similarity of the absorption curves in donor and non-donor solvents suggests that discrete molecules of addition complex are not present in solutions of dinitrogen tetroxide in donor solvents, and therefore the question as to whether the molecular ratios formed in the solid complexes persist in the liquid state does not arise. The concept of partial electron-transfer, with each tetroxide molecule having similar environment in solution, adequately explains physical properties such as vapour pressure, viscosity, and

thermal properties of mixtures. (It should be noted that tetroxide absorption is influenced by solvents to a greater extent at wavelengths below the 343 mμ band. It is possible that molecular association of the kind envisaged gives rise to absorption bands at wavelengths below the range experimentally available.) It is also easy to accept the fact that after partial electron-transfer from a solvent molecule the tetroxide molecule should follow a different mechanism in its reactions with organic compounds.[9] Reactions of tetroxide–donor solvent mixtures with metals is less readily understood. To explain these observations (*e.g.*, that copper does not react with either dinitrogen tetroxide or ethyl acetate, but reacts vigorously with the mixture) it is still necessary to postulate the presence of ionic species $(Don)_nNO^+\cdot NO_3^-$, which are present in too small a concentration to modify the ultraviolet absorption spectrum. In such species the question of a value for n is not irrelevant, and there is evidence from conductivity measurements that it may exceed unity.[10,11] The only evidence that the ionic concentration is very high is from spectroscopic measurements on diethylnitrosamine–dinitrogen tetroxide mixtures.[11] On re-examination, however, it appears that absorption by the nitrosamine, which was used in

FIG. 5. *Influence of NO_2 on optical density of N_2O_4 solutions in* n- *or* cyclo-*hexane.*

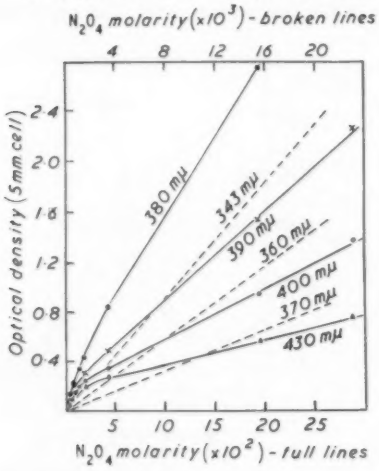
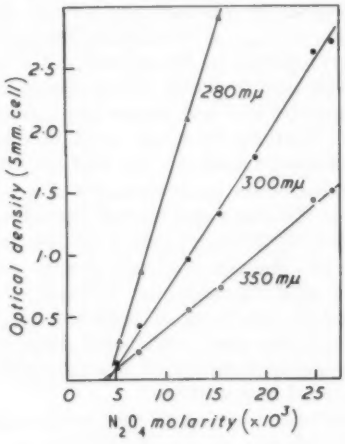


FIG. 6. *Optical density of N_2O_4 solutions in* 1 : 4-*dioxan.*



the compensating cell, was so high at 415 mμ as to render spurious the absorption band at this wavelength believed to be due to the co-ordinated NO^+ ion.

In connection with measurements on the ultraviolet absorption spectrum of nitroparaffins, alkyl nitrates, and alkyl nitrates, Ungnade and Smiley[12] report that solutions of " nitrogen dioxide " in ether (obtained by direct dissolution of dinitrogen tetroxide in ether, and consequent dilution with ether) absorb in the same region as the nitrites, and that there are five pronounced vibrational fine-structure bands. Their curve is similar to that for nitrous acid in strongly acid aqueous solutions,[13] but resembles even more closely the curve obtained when solutions of dinitrogen tetroxide in organic solvents are contaminated with water. We therefore consider that the curve in Fig. 2, which shows

[9] Levy and Scaife, *J.*, 1946, 1093, 1096, 1100.
[10] Addison, Conduit, and Thompson, *J.*, 1951, 1303.
[11] Addison and Conduit, *J.*, 1952, 1390.
[12] Ungnade and Smiley, *J. Org. Chem.*, 1956, **21**, 993.
[13] Singer and Vamplew, *J.*, 1956, 3971; Bayliss and Watts, *Chem. and Ind.*, 1955, 1353; *Austral. J. Chem.*, 1956, **9**, 319.

no apparent fine-structure, is characteristic of dinitrogen tetroxide under fully anhydrous conditions.

Absorption Spectra in Aromatic Solvents.—From a study of solid molecular addition compounds it was possible to identify two types of organic donor. The 'onium donors, of the type discussed above, contain an atom which has one or more lone pairs of electrons available in *s*- and *p*-orbitals, and usually give 2 : 1 compounds with dinitrogen tetroxide. The π-donors, which include aromatic hydrocarbons and their derivatives, give 1 : 1 solid compounds. They have electrons available in molecular orbitals, and form compounds by orbital overlap; this is often evident from reversible colour changes in the solids. The absorption spectra of π-donors (Fig. 4) provide confirmation that the type of electronic interaction differs from that of 'onium donors in the liquid state also. With π-donor solvents, $\lambda_{max.}$ remains unchanged at 343 mμ, but the ε values increase with the strength of the π-donor: chlorobenzene, benzene, toluene, *p*-xylene. As absorption increases, the curve tails into the visible. *p*-Xylene solutions, though colourless at room temperature, become deep red-brown at −20°, and solutions in mesitylene and tetrahydronaphthalene have this colour at room temperature. The last two solvents give dinitrogen tetroxide absorption curves of the *p*-xylene type (Fig. 4), but with much higher ε values; unfortunately a small amount of chemical attack occurs, so that the exact tetroxide concentration in these very dilute tetroxide solutions (and hence the ε values) cannot be determined with accuracy. It is certain, however, that the intense colours arise from orbital overlap rather than chemical decomposition.

Contribution of NO_2 *to Absorption by* N_2O_4 *Solutions.*—The solutions were coloured light brown by the nitrogen dioxide present. Pure liquid dinitrogen tetroxide contains 0·09% by weight of dioxide [6] at 20°, and for ideal solutions this will increase if the tetroxide is diluted by solvents. It was therefore important to determine the extent to which the dioxide present in the solutions might contribute to the absorption. The optical density of solutions has therefore been measured at different molarities (Fig. 5) over a wavelength range covering the 343 mμ band. At wavelengths up to 370 mμ, Beer's law is obeyed closely. The proportion of dioxide in the tetroxide will vary with concentration of the latter, and any significant absorption would result in a deviation from Beer's law. However, absorption by nitrogen dioxide becomes detectable at 380 mμ, and the curvature of the Beer's law plot at low tetroxide concentrations becomes more pronounced with increase in wavelength. In the determination of ε at these higher wavelengths (Figs. 1—4) advantage was taken of the fact that as concentration of dinitrogen tetroxide increases, the relative proportion of nitrogen dioxide decreases, and the curvature of the Beer's law plot ultimately vanishes. The minimum gradient of each curve (Fig. 5) at high tetroxide concentrations was therefore taken to represent the true ε value for dinitrogen tetroxide at that wavelength.

For a given concentration of tetroxide, the depth of the nitrogen dioxide coloration varied widely with the solvent used. It was greatest for paraffins, carbon tetrachloride, and chloroform, and decreased with increasing donor properties of the solvent; ethyl acetate and dioxan solutions were only faintly coloured. The equilibrium $N_2O_4 \rightleftharpoons 2NO_2$ is therefore influenced by change in solvent. Cundall [14] first observed this effect. It is reasonable to assume that partial electron-donation to the tetroxide, which is known to influence its chemical reactions, should also restrict its homolytic dissociation, and it is likely that a list of donor solvents, drawn up in reverse order of the intensity of their colour with dinitrogen tetroxide, would coincide with that drawn up on the basis of vapour-pressure deviations.[2]

Experimental

All measurements were made with a Unicam S.P. 500 spectrophotometer, at a temperature close to 18°. The 5 mm. cells used were of fused silica, with ground stoppers, and were optically matched.

[14] Cundall, *J.*, 1891, 1076; 1895, 794.

Materials.—To obtain the appropriate optical density, it was necessary to employ very dilute tetroxide solutions (as low as 0·002M). It was therefore essential that the solvents should be purified with scrupulous care. This was done by usual procedures, particular care being taken to remove water and those impurities likely to react with dinitrogen tetroxide. For example, thiophen reacts readily, and was removed from aromatic hydrocarbons by sulphuric acid. Carbon tetrachloride was washed with alcoholic sodium hydroxide, to remove hydrogen chloride which reacts to give nitrosyl chloride; acetic anhydride did not give consistent results until it had been refluxed for several hours over sodium and fractionated from it.

Dinitrogen tetroxide was prepared by the method already described,[15] and no further purification was necessary.[16]

Preparation of Solutions.—A small weighed bulb was evacuated on a vacuum-line. About 0·1 g. of dinitrogen tetroxide was condensed into the bulb, which was then sealed off and reweighed. The bulb was transferred to a stout 150 ml. glass bottle containing a weighed quantity (about 100 g.) of pure solvent. The bulb was broken under the solvent and a sample of the stirred solution rapidly transferred to the silica cell in a closed system. This procedure allowed the immediate use of the solution, and by suitable choice of tetroxide weights and solvent volumes no dilution adjustments were necessary. This aspect is of great importance in this work because, in spite of the great care taken in purifying solvents, all solutions deteriorated with time, the optical density usually decreasing. For example, after repeated fractionation from phosphoric oxide, paraffins reacted at such a rate that the absorption fell by about 2% in 10 min. Spectra were therefore recorded immediately after mixing. The absorption spectrum is much more sensitive to this slight deterioration than is any other physical property of the solutions so far examined, and was observed in cases where phase studies, viscosity, volume changes, electrical conductivity, and thermal properties showed no evidence of changes with time.

Despite the appropriate and often lengthy purification adopted for each solvent, it was sometimes impossible to remove final traces of impurity which destroyed some part of the small quantity of tetroxide present in the solutions. This led to a corresponding error in evaluating ε, which was not evident however without examination of the optical density–concentration curves. The procedure adopted to obtain the true extinction coefficient is illustrated in Fig. 6 for dioxan solutions. Optical densities at a particular wavelength were plotted against concentration (determined from added weight) of tetroxide for a series of solutions, a fresh solution being made up for each measurement from the same bulk stock of solvent. Part of the tetroxide is seen to have been destroyed, giving a product which was relatively non-absorbing, since the Beer's law plots gave straight lines which intersected the concentration axis at a positive value. The true ε values were obtained from the slopes of these lines, and are thus independent of the intercept on the axis.

The authors are indebted to the Department of Scientific and Industrial Research for a Maintenance Grant (to J. C. S.).

THE UNIVERSITY, NOTTINGHAM. [*Received, April 28th,* 1958.]

[15] Addison and Thompson, *J.*, 1949, S 218.
[16] Addison, Allen, Bolton, and Lewis, *J.*, 1951, 1289.

638. *Tetracarbonyl Halides of Rhenium.*

By E. W. Abel, G. B. Hargreaves, and G. Wilkinson.

The three rhenium tetracarbonyl halides $[Re(CO)_4X]_2$ (X = Cl, Br, I), prepared by thermal decomposition of the corresponding pentacarbonyl halides, with elimination of carbon monoxide, have been shown to be dimeric by molecular-weight determinations. They are reconverted into the pentacarbonyl halides by carbon monoxide at high temperature and pressure. The tetracarbonyl iodide reacts with pyridine to give the monomeric bispyridinerhenium tricarbonyl iodide, which is identical with the product obtained by the action of pyridine on rhenium pentacarbonyl iodide. The structures of these compounds are discussed, and the carbonyl stretching frequencies in the infrared spectra are recorded.

Rhenium pentacarbonyl halides $[Re(CO)_5X]$ were first prepared by Schulten [1] by the action of carbon monoxide on the corresponding hexahalogenorhenates. They were also prepared by Heinz and Leschewski [2] and by Hieber, Schuh, and Fuchs.[3] The latter reported the monomeric nature of these compounds, and stated that rhenium carbonyl halides with lower carbonyl content than the pentacarbonyl halides were not produced.

By thermal decomposition of the rhenium pentacarbonyl chloride, bromide, and iodide, we have now produced the corresponding rhenium tetracarbonyl halides:

$$2Re(CO)_5X = [Re(CO)_4X]_2 + 2CO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Molecular-weight determinations have shown that these compounds are dimeric. The reaction can be carried out by careful heating of the pentacarbonyl halide alone, but, in view of difficulties due to sublimation of the compounds, the reaction was best carried out by refluxing the pentacarbonyl halide in a high-boiling inert solvent. The progress of the dimerization was shown by the rate of evolution of carbon monoxide, and the reaction appeared to be fastest for the iodide and slowest for the chloride, in accordance with the reported order of chemical reactivity.[3]

These dimeric rhenium tetracarbonyl halides are sparingly soluble in organic solvents but can be recrystallized with difficulty from chloroform or *cyclo*hexane. They decompose on heating without melting. The chloride and bromide form fine white crystals, but the iodide crystallizes in the form of long needles whose yellow colour undoubtedly accounts for the slight yellow colour of rhenium pentacarbonyl iodide reported previously.[1,2,3] Very pure samples of the latter, prepared both by Brimm *et al.*[4] and by us, are white. Schuh [5] has observed that rhenium pentacarbonyl iodide in hexane decomposes in ultraviolet light to give a yellow solution, the spectrum of this decomposition product being similar to that of the dimeric rhenium carbonyl. Thus Schuh probably observed the spectrum of the dimeric carbonyl iodide, and we have shown that the dimeric iodide is indeed produced by irradiation of hydrocarbon solutions of the monomer.

Nitric oxide under normal conditions does not react with rhenium tetracarbonyl halides. Carbon monoxide, however, under conditions of high temperature and pressure, breaks the dimeric bridge structure to re-form the monomeric pentacarbonyl halide; reaction (1) is thus reversible, depending upon the experimental conditions.

The most reasonable structure for the tetracarbonyl halides is (I), in which there is a conventional halogen bridge as, for example, in the well-known carbonyl halides of platinum and ruthenium. The infrared spectra of the compounds in the carbonyl region (Table 1) are consistent with this formulation. Other possibilities would involve a carbonyl

[1] Schulten, *Z. anorg. Chem.*, 1939, **243**, 164.
[2] Heinz and Leschewski, *ibid.*, 1941, **248**, 164.
[3] Hieber, Schuh, and Fuchs, *ibid.*, p. 243.
[4] Brimm, Lynch, and Sesney, *J. Amer. Chem. Soc.*, 1954, **76**, 3831.
[5] Schuh, *Z. anorg. Chem.*, 1941, **248**, 276.

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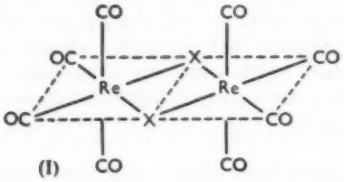
bridge (although carbonyl stretching frequencies in the accepted bridging region are not observed) or a structure involving a metal–metal bond.

Infrared spectra of rhenium carbonyl halides.

Compound	Solvent	Carbonyl stretching modes (cm.$^{-1}$)	Compound	Solvent	Carbonyl stretching modes (cm.$^{-1}$)
$Re(CO)_5Cl$	CCl_4	2056, 1987	$[Re(CO)_4Cl]_2$	$CHCl_3$	2043, 2010, 1964
$Re(CO)_5Br$	CCl_4	2057, 1993	$[Re(CO)_4Br]_2$	$CHCl_3$	2044, 2012, 1970
$Re(CO)_5I$	CCl_4	2055, 1995	$[Re(CO)_4I]_2$	$CHCl_3$	2042, 2012, 1971
			$(C_5H_5N)_2Re(CO)_3I$ ...	CCl_4	2041, 1934, 1891

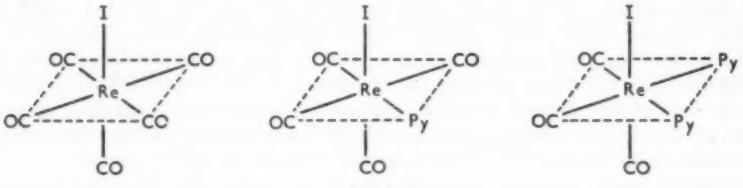
Hieber and Fuchs [6] reported the reaction of the rhenium pentacarbonyl halides with certain tertiary amines at high temperature to produce amine substitution products. We have found it possible to prepare the bis-pyridine compound $(C_5H_5N)_2Re(CO)_3I$ under mild conditions by the direct action of pyridine on both rhenium penta- and tetra-carbonyl iodides. The latter however reacted faster, presumably owing to the ease of attack on the halogen bridge by the amine.



(I)

The configuration of the amine substitution product can be reasonably deduced by considering the nature of the ligands present and their relative ability to form multiple bonds and produce the *trans*-effect.[7,8]

In the carbonyl halide (II), the carbonyl groups predicted to be most labile are those *cis* to the iodine atom, as iodine has the lower *trans*-effect. The first substitution product (III) may be presumed to be an intermediate in the reaction, but attempts to isolate it failed. In (III) the active carbonyl groups are those *cis* to both pyridine and iodine, as both of these have considerably lower *trans*-effects than the carbonyl group,[7] which leads to the structure (IV) for the final bis-pyridine compound. A similar argument can be



(II) (III) (IV)

used to show that the product obtained from pyridine and the dimeric tetracarbonyl iodide should also have structure (IV). The products were identical in both cases. In the thermal or photochemical decomposition of the pentacarbonyl iodide to give the dimer, a carbon monoxide group *cis* to the iodine will be the one most readily removed.

Attempts to substitute further carbon monoxide groups in compounds such as $(C_5H_5N)_2Re(CO)_3I$ have failed; with three essentially non-accepting ligands present, the metal–carbon multiple-bond character will be at a maximum since the carbon

[6] Hieber and Fuchs, *Z. anorg. Chem.*, 1941, **248**, 269.
[7] Chatt, Duncanson, and Venanzi, *J.*, 1955, 4456.
[8] Orgel, *J. Inorg. Nuclear Chem.*, 1956, **2**, 137.

monoxide ligands will have essentially exclusive use of the d_ϵ orbitals for multiple-bond formation and the stability of such complexes both thermally and towards further substitution is in accord with this.

Several attempts by different methods to prepare a rhenium carbonyl fluoride from potassium hexafluororhenate were made, but none was successful. Small quantities of rhenium carbonyl, however, were isolated from the reaction between the fluororhenate and carbon monoxide in the presence of aluminium; thus the carbonyl fluoride may have been formed as an intermediate in this reaction. Similarly all attempts to prepare a rhenium carbonyl cyanide from potassium cyanorhenate [$K_3Re(CN)_8$] failed.

Experimental

Microanalyses and molecular weights are by the Microanalytical Laboratories, Imperial College, London.

Preparations and Techniques.—The light petroleum (b. p. 100—120°) was carefully distilled. The rhenium pentacarbonyl halides were prepared by the previous methods.[1,2,3] Molecular weights were determined ebullioscopically in benzene.

Infrared spectra were taken (in CCl_4 or $CHCl_3$) on a Perkin-Elmer Model 21 spectrophotometer with sodium chloride optics.

Decomposition of Rhenium Pentacarbonyl Iodide.—The pentacarbonyl iodide (57·8 mg.) was dissolved in light petroleum (50 c.c.) to give a colourless solution which when refluxed for 10 min. became pale yellow. Further refluxing (2 hr.) caused the deposition of fine yellow crystals and the evolution of carbon monoxide. When no further gas was evolved, solvent was removed (25°/0·2 mm.); the yellow crystalline residue was recrystallized from boiling chloroform to give *rhenium tetracarbonyl iodide* (45·2 mg., 83%) (Found: C, 11·1; O, 15·3; I, 30·1%; *M*, 801. $C_8O_8I_2Re_2$ requires C, 11·3; O, 15·1; I, 29·8%; *M*, 850).

This reaction was repeated in the absence of solvent, by heating rhenium pentacarbonyl iodide (43·5 mg.) in an open flask in an oven (130°). After 5 hr. the white crystals had completely changed to rhenium tetracarbonyl iodide (22·7 mg., 55%) (Found: C, 11·4; O, 15·4%). The low yield was due to sublimation of the volatile pentacarbonyl iodide before decomposition.

Decomposition of Rhenium Pentacarbonyl Bromide.—The pentacarbonyl bromide (123·6 mg.) was refluxed for 5 hr. in light petroleum (as above). After removal of solvent and recrystallization from boiling chloroform, *rhenium tetracarbonyl bromide* was obtained (95·3 mg., 80%) (Found: C, 12·9; O, 17·1; Br, 21·0%; *M*, 722. $C_8O_8Br_2Re_2$ requires C, 12·7; O, 16·9; Br, 21·1%, *M*, 756).

Decomposition of Rhenium Pentacarbonyl Chloride.—The pentacarbonyl chloride (285 mg.) was refluxed for 10 hr. in light petroleum (as above). After removal of solvent (20°/0·1 mm.) and recrystallization from boiling *cyclo*hexane *rhenium tetracarbonyl chloride* was obtained (235 mg., 86%) (Found: C, 14·9; O, 19·6; Cl, 10·0%; *M*, 687. $C_8O_8Cl_2Re_2$ requires C, 14·4; O, 19·2; Cl, 10·6%; *M*, 667).

Interaction of Rhenium Tetracarbonyl Iodide and Carbon Monoxide.—The very finely powdered tetracarbonyl iodide (93·7 mg.) was heated in carbon monoxide (150°/200 atm.). After cooling, a fall in pressure was observed. The contents of the autoclave were extracted with benzene and the solution filtered; removal of solvent from the colourless filtrate left white crystals. Sublimation (60°/0·1 mm.) yielded rhenium pentacarbonyl iodide (82·1 mg., 82%) [Found: C, 13·5; I, 27·8%; *M* (cryoscopic in benzene), 477. Calc. for C_5O_5ReI: C, 13·3; I, 28·0%; *M*, 453].

Interaction of Rhenium Tetracarbonyl Iodide and Pyridine.—The tetracarbonyl iodide (76·3 mg.) was suspended in pyridine (2 c.c.) and the mixture gently warmed under reflux. As the liquid boiled there was a rapid evolution of carbon monoxide. Heating was continued (30 min.) until gas was no longer evolved. After removal of solvent (20°/0·1 mm.) the pale yellow crystalline residue was recrystallized from chloroform to give pure bispyridinerhenium tricarbonyl iodide (78·4 mg., 79%) (Found: C, 28·4; H, 1·7; O, 8·9; N, 5·2; I, 22·5%; *M*, 598. Calc. for $C_{13}H_{10}O_3N_2ReI$: C, 28·1; H, 1·8; O, 8·6; N, 5·1; I, 22·8%; *M*, 555).

Interaction of Rhenium Pentacarbonyl Iodide and Pyridine.—The pentacarbonyl iodide (103·5 mg.) in pyridine (5 c.c.) was refluxed gently for 5 hr., after which no more carbon monoxide was evolved. Removal of solvent (20°/0·1 mm.) left pale yellow crystals which were

recrystallized from chloroform to give bispyridinerhenium tricarbonyl iodide (91·5 mg., 72%) (Found: C, 28·3; H, 1·8; N, 4·9%; *M*, 586).

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INORGANIC CHEMISTRY LABORATORIES,
IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W.7.

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639. *Mechanism of the Kolbe–Schmitt Reaction. Part II.*[1] *Influence of the Alkali Metal.*

By S. E. HUNT, J. IDRIS JONES, A. S. LINDSEY, and (in part) D. C. KILLOH and H. S. TURNER.

A study has been made of the behaviour on heating of the alkali-metal mono- and di-salicylates and *p*-hydroxybenzoates, and of some related substances. Some rate studies are reported for these reactions.

When a mixture of ^{14}C-labelled potassium carbonate and dipotassium salicylate was heated at 200° appreciable exchange accompanied the rearrangement with formation of labelled *p*-hydroxybenzoate. The mechanism of these reactions is discussed

DIFFERENCES in behaviour of the alkali metals in organic reactions have often been noted.[2,3,4] The Kolbe–Schmitt reaction provides a classical example.[1,2,5,6]

In 1875 Kolbe [7] and Ost [8] drew attention to the remarkable difference in behaviour between sodium and potassium salicylate at 220°. The former yielded disodium salicylate, the latter dipotassium *p*-hydroxybenzoate. There occur in the literature many conflicting reports concerning the thermal rearrangement of the alkali-metal salts of aromatic hydroxy-carboxylic acids. In large measure, these are due to the use of carbon dioxide as a supposedly inert atmosphere in the early studies of these rearrangements,[9,10] for under these conditions it is possible for carboxylation to intervene.

More recent studies have revealed differences not only in the ratio of *ortho*- to *para*-substitution, but also in the extent of carboxylation and in the tendency to form hydroxydicarboxylic acids, particularly at higher temperatures.[6,11] In the Marasse procedure also differences have been observed [11,12,13] and these distinctions hold in the phenol, naphthol, and heterocyclic series.[6]

In order to establish how far purely thermal rearrangements are involved in the Kolbe–Schmitt reaction, a study of the behaviour on heating of various alkali-metal derivatives of salicylic acid and other aromatic hydroxy-carboxylic acids was undertaken.

Most of our experiments were conducted *in vacuo*; this served to minimise oxidation, and in those cases where carbon dioxide was evolved eliminated the possibility of recarboxylation. From our studies on the monoalkali-metal salts the following facts have emerged. Monosodium salicylate at 300° yields equimolecular amounts of phenol, carbon dioxide, and disodium salicylate. A mixture of sodium phenoxide and monosodium salicylate at 140° gives equimolecular amounts of free phenol and disodium salicylate.

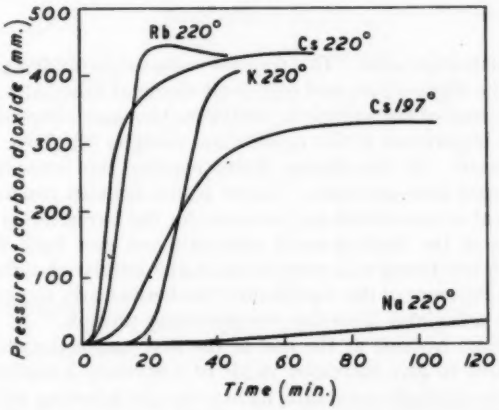
[1] Part I, *J.*, 1954, 3145.
[2] Brady and Jakobovits, *J.*, 1950, 767.
[3] Morton and Letsinger, *J. Amer. Chem. Soc.*, 1945, **67**, 1537.
[4] Brändström, *Arkiv Kemi*, 1953, **6**, 155; 1954, **7**, 81; *Acta Chem. Scand.*, 1953, **7**, 223.
[5] Widequist, *Arkiv Kemi*, 1954, **7**, 229.
[6] Lindsey and Jeskey, *Chem. Rev.*, 1957, **57**, 583.
[7] Kolbe, *J. prakt. Chem.*, 1875, **11**, 24.
[8] Ost, *ibid.*, 1875, **11**, 385.
[9] Kupferberg, *ibid.*, 1876, **13**, 103.
[10] den Velden, *ibid.*, 1877, **15**, 151.
[11] Baine, Adamson, Barton, Fitch, Swayampati, and Jeskey, *J. Org. Chem.*, 1954, **19**, 510.
[12] Cameron, Jeskey, and Baine, *ibid.*, 1950, **15**, 233.
[13] Wessely, Benedikt, Benger, Friedrich, and Prillinger, *Monatsh.*, 1950, **81**, 1071.

Monosodium *p*-hydroxybenzoate at 250° gives substantially disodium *p*-hydroxybenzoate, together with phenol and carbon dioxide.

In contrast monopotassium salicylate at 250° yields phenol, carbon dioxide, and *p*-hydroxybenzoic acid with small amounts of 4-hydroxy*iso*phthalic and 6-hydroxytrimesic acid and unchanged salicylic acid. The same products are obtained by heating equimolecular mixtures of mono-sodium and -potassium salicylate. However monopotassium *p*-hydroxybenzoate at 340° gives dipotassium *p*-hydroxybenzoate, phenol, and carbon dioxide.

The thermal decomposition of mono-lithium, -sodium, -potassium, -rubidium, and -cæsium salicylate at fixed temperatures was also examined in a closed, partly evacuated system, the extent of decomposition being measured by the carbon dioxide pressure. The results are presented graphically in Figs. 1 and 2. The threshold temperature for the decomposition decreases and the rate of decomposition at any one temperature increases

FIG. 1.

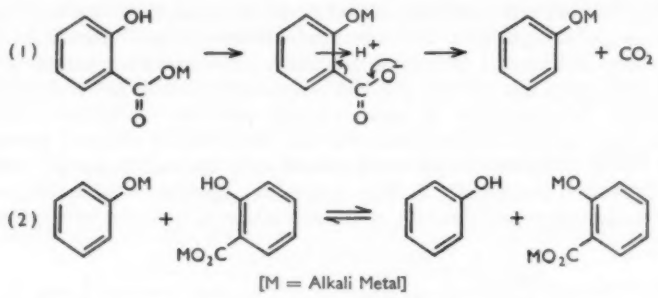


through the series Li, Na, K, Rb, Cs. The slight decrease in pressure towards the end of some experiments suggests that some recarboxylation occurs at this stage. From the lithium and sodium salts only salicylic acid was detected in the products; in the cases of potassium, rubidium, and cæsium, the product was substantially *p*-hydroxybenzoic acid.

The thermal decomposition of the monoalkali-metal salicylates, as well as of monosodium and -potassium *p*-hydroxybenzoate, probably proceeds by heterolysis of the anionic form after migration of the metal cation.[14] Some support for this view is given by the observation that heating monosodium salicylate in phenol leads to almost complete decarboxylation. The second stage involves reaction of the metal phenoxide with a second molecule of the metal salicylate to yield phenol and the dimetal salicylate, which itself may undergo rearrangement when the metal is potassium, rubidium, or cæsium. In the case of sodium this second step occurs at temperatures as low as 140° and presumably occurs to a slight extent during the industrial synthesis of salicylic acid from sodium phenoxide and carbon dioxide. The possibility of intermolecular transfer of the CO_2Na unit in the second stage may be excluded since, for example, when a mixture of monosodium salicylate and sodium *p*-tolyloxide is heated only free *p*-cresol is obtained. In reactions with monopotassium salicylate intermolecular transfer has frequently been observed. Thus, Isemer [15] has shown that 2-hydroxy-3-phenylbenzoic acid accompanies *p*-hydroxybenzoic acid when monopotassium salicylate is heated with the potassium derivative of 2-hydroxydiphenyl. Similarly, we have found that, in addition to *p*-hydroxybenzoic acid and small amounts of salicylic acid, 6-hydroxytrimesic acid is obtained when

[14] Brown, *Quart. Rev.*, 1951, **5**, 131.
[15] Isemer, Doctoral Thesis, Halle, 1951.

tripotassium 4-hydroxy*iso*phthalate is heated with monopotassium salicylate; 3-carbamoyl-4-hydroxybenzoic acid is obtained from salicylamide, and 3-phenyl hydrogen



4-hydroxy*iso*phthalate from salol. This transfer is almost certainly a part of the subsequent rearrangement of the dipotassium and higher alkali-metal salicylates, and it has not been observed in the absence of the salicylate–*p*-hydroxybenzoate conversion.

In the past the importance of the equilibrium reaction (2) above has not always been sufficiently appreciated. In the original Kolbe reaction this accounts for the conversion of only half the phenol into salicylate. Under Kolbe–Schmitt conditions the equilibrium determines the extent of conversion and accounts for the formation of certain by-products, since carboxylation of the dialkali-metal salicylate can give both 2- and 4-hydroxy*iso*phthalic acid which are found as by-products in the industrial carboxylation of sodium phenoxide.[16] The existence of this equilibrium has been clearly recognised in the synthesis of long-chain alkyl salicylates from the corresponding phenols.[17]

Addition of sodium hydride at the end of the first carboxylation stage of 2-naphthol has also been claimed to give increased yields of 2-hydroxy-3-naphthoic acid.[18]

Our studies on the dialkali-metal salts have given the following information. Contrary to the claims of Kupferburg,[9] disodium salicylate remains unchanged at 360°. Dipotassium salicylate, however, undergoes the well-known rearrangement to dipotassium *p*-hydroxybenzoate [19] at 200—240°. That the product is dipotassium *p*-hydroxybenzoate and not some complex which when dissolved in water and acidified gives *p*-hydroxybenzoic acid was established by the identity of its infrared spectrum with that of authentic dipotassium *p*-hydroxybenzoate. The reaction, however, is subject to a number of factors which have been disregarded previously. One is the influence of moisture. The dipotassium derivative when prepared from aqueous solutions contains water of crystallisation which is difficult to remove completely. In the present work very dry specimens of the dipotassium salt were prepared and all manipulations were carried out in a dry box. There was no detectable rearrangement when the dry salt was heated at 250°/0·1 mm. for 6 hr. but a trace of phenol was liberated. After exposure of the sample to the atmosphere for a short time rearrangement proceeded readily, as was also the case with less rigorously dried dipotassium salicylate. The main product of the rearrangement was *p*-hydroxybenzoic acid accompanied by small amounts of 4-hydroxy*iso*phthalic and 6-hydroxytrimesic acid. The results of a kinetic study of the rearrangement of dipotassium salicylate at 250° are shown graphically in Fig. 3. The sigmoid curve is typical of a solid-state autocatalytic reaction. Invariably traces of phenol sublimed from the system during the rearrangement and phenol may well serve as a catalytic factor.

A limited study has also been made of the effect of substituents in the benzene ring on

[16] Hunt, Jones, and Lindsey, *J.*, 1956, 3099.
[17] B.P. 738,359/1955.
[18] B.P. 736,476/1955.
[19] *Org. Synth.*, Coll. Vol. II, 1943, p. 341.

the rearrangement products. Heating disodium or dipotassium 4-hydroxy*iso*phthalate at 250° for 6 hr. led in the former case to decomposition with partial conversion into salicylic and 6-hydroxytrimesic acid, in the latter case to partial conversion into *p*-hydroxybenzoic and 6-hydroxytrimesic acid. Heating dipotassium 3-methyl-2-hydroxybenzoate (*o*-cresotinate) under the same conditions gave the potassium derivatives of 4-hydroxy-5-methyl-benzoic and -*iso*phthalic acid. The rearrangement was analogous therefore to that of dipotassium salicylate, the presence of the dicarboxylic acid suggesting an easier transfer of carboxylate group. Carboxylation of potassium *o*-tolyloxide with carbon dioxide under pressure [20] led to the formation of *o*-cresotinic and 4-hydroxy-5-methyl-*iso*phthalic acid in approximately equal quantities, together with a small amount of

FIG. 2.

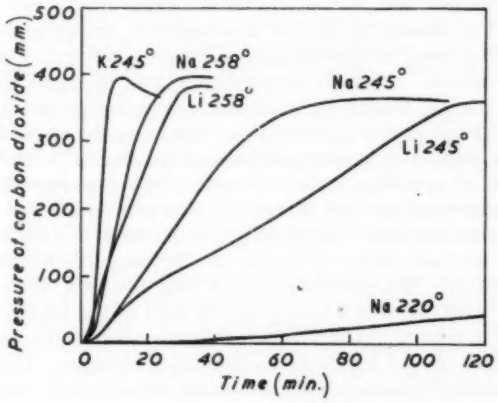
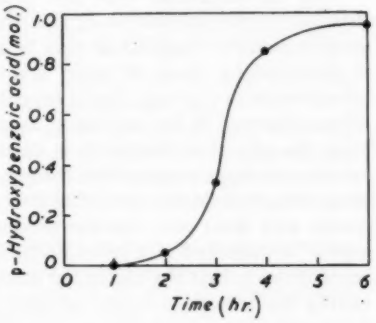


FIG. 3.



4-hydroxy-5-methylbenzoic acid. Heating 4-amino-2-hydroxypotassium benzoate at 160° led to decarboxylation with formation of free and bound *m*-aminophenol; no acidic product was obtained other than a little unchanged 4-aminosalicylic acid.

In order to study the mechanism, a tracer investigation of the rearrangement of dipotassium salicylate in admixture with potassium [^{14}C]carbonate was undertaken (by H. S. T. and D. C. K.). In a vacuum (0·1 mm.) pure dry dipotassium salicylate either alone or in admixture with approximately 5% of potassium carbonate was unchanged after 6 hr. at 250°, but at 200° in an atmosphere of dry nitrogen the rearrangement could be carried out reproducibly to 50% completion in about 30 min. Even in the presence of carbonate, rearrangement was always accompanied by a loss in weight of about 5%, most of which was due to free phenol distilling from the mixture. The product was worked up for *p*-hydroxybenzoic acid and carbon dioxide (from the carbonate). It was found that exchange had occurred to about 4·7% of the maximum (assuming the carboxylate group alone to be capable of exchange). In blank experiments (i) in which the original mixture was worked up without having been heated and (ii) in which the working up procedure was applied to a mixture of dipotassium *p*-hydroxybenzoate and [^{14}C]carbonate the extent of apparent exchange was negligible, less than 0·005% of the activity in the carbonate being found in either acid. Although an intimate mixture of the salicylate and carbonate was prepared by grinding, it is obvious that at the molecular level the mixture must have been extremely heterogeneous. An overall exchange of about 5% may therefore correspond to extensive, if not complete, exchange in the regions of intimate contact.

Ost [8] reported that conversion of dipotassium salicylate into *p*-hydroxybenzoate was

[20] Ihle, *J. prakt. Chem.*, 1876, **14**, 443.

inhibited at 250° by the addition of a further mol. of potassium hydroxide. We have detected no rearrangement after heating an equimolecular mixture of dipotassium salicylate and potassium methoxide at 250° for 6 hr. However, a similar mixture, after 6 hr. at 340°, contained *p*-hydroxybenzoic and 4-hydroxy*iso*phthalic acid, in addition to unchanged salicylic acid. It is significant that in the commercial preparation of *p*-hydroxybenzoic acid from dipotassium salicylate it is customary to use a small excess of potassium hydroxide. Further, we have observed that addition of 5% of potassium carbonate has no noticeable effect on the rate of rearrangement. This evidence suggests that the reaction is not proton-catalysed. The inhibition of the rearrangement as a result of adding 1 mol. of potassium methoxide or hydroxide may be due to the formation of an ortho-salt *o*-KO·C_6H_4·C(OK)$_2$·OMe or *o*-KO·C_6H_4·C(OK)$_2$·OH. It is pertinent that phenyl-lithium interacts with lithium benzoate to give $Ph_2C(OLi)_2$ [21] and Bender [22] has demonstrated the existence of addition compounds of carboxylic acid derivatives with sodium alkoxides.

Our investigations were not taken far enough to permit a completely unequivocal decision on the mechanism of the rearrangement of dipotassium salicylate. Nevertheless some reasonable suggestions may be advanced. We have demonstrated that the reaction is catalysed by traces of water and of phenol, that it is facilitated by electron-releasing substituents in the ring, that it is probably not proton-catalysed (in contrast to the marked effect observed in the analogous rearrangement of aminonaphthalenesulphonates [23]), and that the migrating fragment is capable of exchange with carbonate. Our experiments *in vacuo* strongly suggest that the rearrangement does not proceed by way of a decarboxylation–recarboxylation involving free carbon dioxide. Apart from the isolation of a little oxalic acid from one reaction product we have failed to isolate the by-products which would be expected in a free-radical reaction. We therefore suggest that the most likely mechanism is that the migrating group is $^+CO_2K$, which is only loosely held to the nucleus during the transition stage, perhaps by a π-bond. The reaction may be either intra- or inter-molecular, depending on the precise spatial relation of adjoining molecules. The group $^+CO_2K$ will, on this view, be capable of exchange with carbonate, though under the conditions of our tracer experiments extensive overall exchange would not be expected. It is highly probable that similar considerations apply to the rearrangements of alkali-metal salts of unsubstituted aromatic carboxylic acids recently reported by Raecke.[24] We have discussed the mechanism of this reaction and some views upon it in a recent memoir.[25]

Chelation has been postulated in the alkali-metal salicylates [26] and Widequist [5] has suggested that the difference in behaviour of the alkali-metal salicylates towards heat could be related to the chelating tendency of the cations. Martel and Calvin [27] have pointed out that the chelating strengths can be correlated with the e^2/r values of the ions. For the alkali-metal ions the values are Li^+ 1·7, Na^+ 1·05, K^+ 0·75, Rb^+ 0·68, Cs^+ 0·60. Lithium and sodium salicylate, which do not rearrange, are more strongly chelated than the potassium, rubidium, and cæsium salts. Some evidence for the participation of a chelation effect is given by the results obtained by heating (i) a mixture of monosodium salicylate and potassium phenoxide at 245° and (ii) a mixture of monosodium salicylate and potassium carbonate at 250°. In both cases an appreciable quantity of *p*-hydroxybenzoic acid was found in the product, indicative of the intermediate formation of *o*-KO·C_6H_4·CO_2Na with subsequent rearrangement. A mixture of dipotassium *p*-hydroxybenzoate and disodium salicylate, both of which are thermally stable alone at 340°, when

[21] Bluhm, Donn, and Zook, *J. Amer. Chem. Soc.*, 1955, **77**, 4406.
[22] Bender, *ibid.*, 1953, **75**, 5986.
[23] Shilov, Bogdanov, and Shilov, *Doklady Akad. Nauk S.S.S.R.*, 1953, **92**, 93.
[24] Raecke, *Angew. Chem.*, 1958, **70**, 1.
[25] Jones, Lindsey, and Turner, *Chem. and Ind.*, 1958, 659.
[26] Sidgwick, "The Electronic Theory of Valency," Oxford, 1927, p. 242.
[27] Martel and Calvin, "Chemistry of the Metal Chelate Compounds," Prentice-Hall, New York, 1952, p. 191.

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heated at 320° for 6 hr. gave a product containing appreciable amounts of 4-hydroxy-*iso*phthalic and 6-hydroxytrimesic acid. Thermal migration of carboxylate groups must therefore arise consequent on interchange of cations.

In addition to the chelation effect it is possible that other effects, notably polarisation effects, are also operative. Clearly further studies are needed before the precise mechanism of these solid-state reactions can be elucidated.

Experimental

General.—Microanalyses were carried out by Miss M. Corner and her staff of this laboratory.

Ultraviolet absorption spectra were measured for ethanolic solutions with a Unicam S.P. 500 spectrophotometer, which had been calibrated against an alkaline solution of potassium chromate.[28]

Infrared measurements were made on a modified Hilger D 209 double-beam instrument.[29]

Hygroscopic materials were weighed and manipulated in a dry box.

Preparation of Materials.—Monolithium, monosodium, and monopotassium salicylate were of reagent grade (B.D.H.) quality. After drying at 130° *in vacuo* satisfactory alkali-metal analyses were obtained.

Disodium salicylate was prepared by heating the monosodium salt at 300° for 6 hr. *in vacuo*. The identity of the product was confirmed by infrared spectroscopy.

Most other salts were prepared by neutralisation of aqueous or aqueous-alcoholic solutions, followed by evaporation and drying at 140° *in vacuo*. Dipotassium salicylate and dipotassium *o*-cresotinate were particularly difficult to dry and so were prepared by reaction of anhydrous methanolic solutions of potassium methoxide and the dry acid. Good analyses were obtained in all cases.

Thermal Rearrangement Experiments.—The salts were heated in a Pyrex tube which was attached by a cone-and-socket joint to a tared U-tube. The latter was packed in powdered carbon dioxide. A vacuum was applied, *ca.* 0·1 mm. (oil-pump) or 16 mm. (water-pump). Experiments carried out at the latter pressure are marked W.P. in the Tables.

Procedure for Separation of Products.—The solid residue was dissolved in water and made up to a standard volume. "Bound phenol" (present as a metal phenoxide) was liberated from an aliquot portion by passage of carbon dioxide, and recovered by continuous ether-extraction.

Acidification of the aqueous phase followed by continuous ether-extraction and then by removal of the solvent and drying gave the total acids, which were then separated by silica-gel chromatography. The mixed acids (*ca.* 400 mg.) were washed on to the column and eluted with dry benzene. Fractions of 100 ml. each were collected, and the solid acids recovered by evaporation of the solvent. The column was successively washed with 5, 10, 12, 15, and 50% ether in benzene, then with 100% ether, and finally with anhydrous methanol.

The solid acids were identified by m. p. and coloration with ferric chloride solution. Efficient and quantitative separation of salicylic, *p*-hydroxybenzoic, 4-hydroxy*iso*phthalic, and 6-hydroxytrimesic acid was attained in this way.

Effect of Phenol on the Decomposition of Monosodium Salicylate.—Monosodium salicylate (8·8 g.) was boiled with excess of phenol (52·3 g.) for 5 hr., then cooled. Water was added and the free phenol removed by steam-distillation. "Bound" phenol (5·7 g.) and salicylic acid (0·15 g.) (confirmed by ferric chloride test and m. p.) were isolated as before. Thus 98% decarboxylation had occurred.

Carboxylation of Salicylamide using Monopotassium Salicylate.—An intimate mixture of salicylamide (0·1 mole) and monopotassium salicylate (0·1 mole) was heated slowly to 220° and kept there for 1¼ hr. Frothing occurred and phenol distilled, the pressure being reduced at the end to assist the removal of phenol. The residue was dissolved in water and ether-extracted. Acidification of the aqueous phase gave a coloured precipitate (13·2 g.) from which crude *3-carbamoyl-4-hydroxybenzoic acid* was isolated, m. p. 297° (decomp.) after recrystallisation from dioxan (Found: C, 53·3; H, 4·0; N, 7·4. $C_8H_7O_4N$ requires C, 53·0; H, 3·9; N, 7·7%).

Carboxylation of Phenyl Salicylate using Monopotassium Salicylate.—Phenyl salicylate

[28] Haupt, *J. Res. Nat. Bur. Stand.*, 1952, **48**, 414.
[29] Hale, *J. Sci. Instr.*, 1949, **26**, 359; 1953, **30**, 52.

XUM

Results of thermal rearrangement experiments.

Expt.	Reactant(s) and mols. %	Experimental conditions	Products (mols. %) Phenol Free	Phenol Bound	CO_2	SA	pHBA	4HIPA	6HTA
1	A(100)	360°/24 hr.; W.P.†	6	—	—	83	—	—	—
2	B(100)	250° raised to 360°/7 hr.; W.P.	50	—	51	50	—	—	—
3	B(100)	300°/6 hr.†	49	—	53	49	—	—	—
4	C(100)	250°/6 hr.	Trace	2	—	—	99	—	—
5	D(100)	250°/6 hr.	10	26	38	—	61	—	—
6	B(50) + E(50)	140°/2 hr.; W.P.	53	—	—	47	—	—	—
7	B(50) + F(50)	140°/6 hr.; W.P.	44 *	3 *	—	48	—	—	—
8	G(100)	250°/1 hr.	<1	—	—	90	—	—	—
9	G(100)	250°/2 hr.	3	2	—	88	5	—	—
10	G(100)	250°/3 hr.	3	1	—	62	34	—	—
11	G(100)	250°/4 hr.	2	2	—	16	85	—	—
12	G(100)	250°/6 hr.	1	3	—	<2	96	—	—
13	G(100)	250°/7 hr.; W.P.	1	23	2	1	51	9	6
14	G(50) + H(50)	250°/6 hr.	—	—	—	47	—	—	—
15	G(50) + H(50)	340°/6 hr.	—	12	—	65	2	4	2
16	G(82) + J(18)	250°/3 hr.; W.P.	12	20	—	29	28	7	—
17	K(100)	250°/7 hr.; W.P.	50	—	32	4	29	10	3
18	K(100)	250°/5 hr.	52	Trace	49	—	48	3	—
19	K(50) + B(50)	250°/7 hr.; W.P.	55	—	50	22	17	6	—
20	K(50) + B(50)	320°/5 hr.; W.P.	51	9	51	6	7	19	3
21	K(50) + L(50)	250°/6 hr. W.P.	29	—	57	1	24	18	18
22	M(100)	340°/6 hr.	53	—	40	—	42	—	—
23	N(100)	250°/6 hr.	10	3	92	6	—	62	8
24	P(100)	250°/6 hr.	15	7	67	—	40	31	7
25	B(50) + R(50)	245°/4 hr.	40	32	55	15	13	—	—
26	B(100) + S(200)	230—250°/0·5 hr. 250—260°/2 hr.	34	4	—	18	41	—	—
27	T(50) + A(50)	320°/6 hr.	Trace	24	2	15	4	35	11

Code:

A Disodium salicylate.
B Monosodium salicylate.
C Disodium *p*-hydroxybenzoate.
D Monosodium *p*-hydroxybenzoate.
E Sodium phenoxide.
F Sodium *p*-tolyloxide.
G Dipotassium salicylate.
H Potassium methoxide.
J Phenol.
K Monopotassium salicylate.
L Tripotassium 4-hydroxy*iso*phthalate.
M Monopotassium *p*-hydroxybenzoate.
N Disodium 4-hydroxy*iso*phthalate.
P Dipotassium 4-hydroxy*iso*phthalate.
R Potassium phenoxide.
S Potassium carbonate.
T Dipotassium *p*-hydroxybenzoate.
SA Salicylic acid.
pHBA *p*-Hydroxybenzoic acid.
4HIPA 4-Hydroxy*iso*phthalic acid.
6HTA 6-Hydroxytrimesic acid.
W.P. Vacuum induced by water-pump.
* *p*-Cresol.
† Some charring occurred.

(42·8 g.) and monopotassium salicylate (70·8 g.) were heated, under slightly reduced pressure, at 240° for 4 hr. Phenol (27 g.) distilled and the residue yielded bound phenol, salol (31 g.), and 3-phenyl hydrogen 4-hydroxy*iso*phthalate (6 g.); after recrystallisation from methanol (charcoal) the acid had m. p. 235° (Found: C, 65·1; H, 4·1. Calc. for $C_{14}H_{10}O_5$: C, 65·1; H, 3·9%).

Rate of Thermal Decomposition of the Monoalkali-metal Salicylates.—The apparatus employed is shown diagrammatically (Fig. 4). The salt (approx. 2 millimoles) was introduced into *A* and spread along the bulb, and the trap *B* cooled to 0° in ice. The system was evacuated to about 20 mm., then tap *C* was turned so as to isolate the system. The bulb *A* was heated to the required temperature in a vapour bath. The liquids used and the temperatures obtained were as follows: diethylene glycol monoethyl ether monoacetate 197°, dipropylene glycol 220°, butyl benzoate 245°, 1 : 6-dimethylnaphthalene 258°. While the reaction was in progress readings were taken of pressure against time. The rates of decomposition, as measured by the rate of evolution of carbon dioxide, of all the alkali-metal salicylates is graphically shown in Figs. 1—3.

The solid residues were worked up. From lithium and sodium salicylate the product was salicylic acid; in the case of potassium, rubidium and cæsium salicylates the ferric chloride test was negative, showing that no unchanged salicylic acid was present, and that no 4-hydroxy*iso*-phthalic acid had been formed. The m. p. and mixed m. p. confirmed the presence of *p*-hydroxy-benzoic acid.

Infrared Spectroscopic Examination of the Solid Products obtained by heating Dipotassium Salicylate.—The infrared spectra of the products from experiments 12 and 18 (Table), and from similar experiments not recorded, were taken from KCl discs. The spectra were compared directly with those of authentic samples of dipotassium salicylate, *p*-hydroxybenzoate, and 4-hydroxy*iso*phthalate, and in each case were closely similar to that of dipotassium *p*-hydroxybenzoate.

Action of Heat on Dipotassium o-*Cresotinate.*—Dipotassium *o*-cresotinate (10 g.) was heated under reduced pressure for 6 hr. at 250°. No loss of weight occurred. The mixed acid obtained from the product was extracted with cold chloroform to remove unchanged *o*-cresotinic acid (confirmed by m. p. and ferric chloride test). Sublimation of the residue under reduced pressure gave a sublimate shown to be 4-hydroxy-3-methylbenzoic acid, m. p. 174—175° (no colour with

FIG. 4.

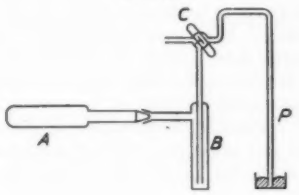
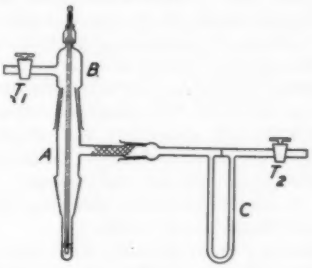


FIG. 5.



alcoholic ferric chloride), by comparison with an authentic specimen (Found: C, 63·0; H, 5·7. Calc. for $C_8H_8O_3$: C, 63·2; H, 5·3%).

Recrystallisation of the non-sublimable residue from ethanol–water gave 4-hydroxy-5-methyl*iso*phthalic acid, m. p. 294—295°, no colour with alcoholic ferric chloride, red colour with aqueous ferric chloride (Found: C, 55·1; H, 4·2. Calc. for $C_9H_8O_5$: C, 55·1; H, 4·1%).

Action of Heat on Potassium 4-Amino-2-hydroxybenzoate.—The salt (10·5 g.) was heated for 6 hr. at 160° *in vacuo* (water-pump). Some *m*-aminophenol (0·4 g.) (m. p. and mixed m. p. 123°) distilled into the trap, and the residue (8·98 g.) in water (100 ml.) was continuously extracted with ethyl acetate to give more *m*-aminophenol (4·5 g.) (m. p. and mixed m. p.). The aqueous phase contained *m*-aminophenol (" bound phenol ") (0·3 g.). After adjustment to pH 4 the aqueous phase was continuously extracted with ethyl acetate, to yield a brown solid [1·55 g.; m. p. 112° (decomp.)] which gave a hydrochloride recrystallising from aqueous ethanol [m. p. 233° (decomp.)]. There was no depression of m. p. on admixture with the hydrochloride of *p*-aminosalicylic acid. The infrared spectrum confirmed the identity.

Isotope Experiments on the Rearrangement of Dipotassium Salicylate.—Preparation of materials. Potassium [^{14}C]carbonate was prepared by absorbing [^{14}C]carbon dioxide in a slight deficiency of 0·1N-potassium hydroxide and adjusted to a suitable specific activity by addition of more potassium carbonate. The solution was evaporated to dryness, ground to a fine powder, and dried at 140° *in vacuo*.

Dipotassium salicylate, prepared as above, was dried at 120°/0·1 mm. for several hours.

Thermal rearrangement. The reaction vessel *A* (see Fig. 5) could be closed for weighing by means of two tapered Polythene plugs. A plug of glass wool in the side-arm prevented the carrying over of particles into the trap *C*. The head *B*, which bore a side-arm through which dry nitrogen could be introduced, also carried an Anschütz thermometer the bulb of which, symmetrically disposed out of contact with the walls of the bottom of *A*, was just covered by the normal charge.

In preparing the charge every effort was made to exclude moisture. The apparatus was rigorously dried and all manipulations were carried out in a dry box over phosphoric anhydride. The dipotassium salicylate (300—400 mg.) and potassium [^{14}C]carbonate (15—20 mg.) were weighed separately in weighing tubes and intimately mixed by grinding for 20 min. in an agate mortar. The mixture was transferred to the bottom of *A* by means of a small funnel with a long stem, and the weight introduced obtained by difference. The head *B* was then attached and the combined unit removed from the dry box and weighed. A current of dry nitrogen was

passed in through T_1 and out through the side-arm of A, which was then connected to the trap C. The air within the powder was replaced by nitrogen by several times evacuating the apparatus and re-admitting nitrogen. The trap C was then cooled to $-80°$ and the lower half of A was lowered into a vapour-bath. After a suitable time at the desired temperature the bath was removed and the mixture cooled rapidly to room temperature. Whenever rearrangement occurred a small sublimate of phenol collected in the side-arm of A. This was caused to pass into C by gentle warming. C was then detached, the side-arm of A closed by a plug, T_1 closed, and the whole re-weighed.

The product, which was usually pink, was washed into a flask with carbon dioxide-free water (total 15 ml.) and diluted with 0·382N-potassium carbonate (10·00 ml.). The flask was attached to an apparatus in which carbon dioxide-free dilute sulphuric acid was added while the carbon dioxide liberated was swept from the cold, stirred solution in a current of nitrogen into a series of traps containing aqueous barium hydroxide at ~95°. The barium carbonate was collected and dried out of contact with atmospheric carbon dioxide. The acid liquors were again made alkaline by addition of a slight excess of potassium hydroxide solution, and a stream of carbon dioxide was passed in order to liberate phenol. After extraction with ether (2 × 15 ml.) the aqueous phase was again acidified with sulphuric acid, and the hydroxy-acid extracted by ether (4 × 15 ml.). The combined extracts were dried by refluxing over anhydrous calcium sulphate in a Soxhlet apparatus, and afterwards evaporated to dryness.

The acids were separated on a " sulphuric acid " column,[39] the progress of the separation being followed by ultraviolet spectroscopy. Salicylic and *p*-hydroxybenzoic acid were cleanly separated. 6-Hydroxytrimesic acid travelled with salicylic acid, and 4-hydroxy*iso*phthalic acid with *p*-hydroxybenzoic acid.

In preliminary experiments it was found that no rearrangement took place *in vacuo* (~0·1 mm.) even at ~250° during 6 hr., but under nitrogen at atmospheric pressure the reaction was about half complete in 30 min. at the temperature of boiling benzyl alcohol. The results were somewhat variable even when the greatest care was taken to exclude moisture.

In a blank run, designed to test the possibility of exchange during working-up, dipotassium salicylate (0·2976 g.) and potassium [^{14}C]carbonate (0·0153 g.) were mixed and the normal procedure followed, with the sole difference that the mixture was not heated. The product from the chromatographic separation was purified by sublimation, giving salicylic acid, m. p. 158—158·5° (0·179 g.; specific activity $3·4 \times 10^{-11}$ curies per millimole). The carbon dioxide had a specific activity of $4·9 \times 10^{-6}$ curies per millimole corresponding to $8·9 \times 10^{-5}$ curies per millimole for the carbonate *before* dilution. Thus the transfer of carbon from carbonate to salicylate during working up was $4·8 \times 10^{-4}$%.

A further rough control was carried out to test the exchange of *p*-hydroxybenzoic acid and potassium carbonate during the solution stages of working up. Here the transfer from carbonate to *p*-hydroxybenzoate was $\sim 2·5 \times 10^{-4}$%.

In the tracer run a mixture of dipotassium salicylate (0·3956 g.) and potassium [^{14}C]carbonate (0·0196 g.) was heated for 30 min. at 202·5°. The loss in weight during the rearrangement was 0·0278 g. The *p*-hydroxybenzoic acid fraction (0·1464 g.) was further purified by sublimation to give the acid (specific activity $3·00 \times 10^{-7}$ curies per millimole), m. p. 214—215° (pure *p*-hydroxybenzoic acid melted at 214·5—215·5° under the same conditions). The carbon dioxide collected had a specific activity of $5·45 \times 10^{-6}$, corresponding to $7·86 \times 10^{-5}$ for the carbonate in the reaction product *before* dilution. If exchange between the carbonate and the carboxyl group of the original salicylate had been complete the specific activity would have been $6·35 \times 10^{-6}$ curies per milliatom of exchangeable carbon, or per millimole of recovered hydroxybenzoic acid. The specific activity observed is therefore equivalent to 4·7% attainment of complete exchange.

We thank Mr. W. Kynaston for measurement of infrared spectra and Messrs. P. F. Epstein and S. E. R. Hiscocks for experimental assistance during the tenure of vacation studentships. The work reported formed part of the programme of the Chemical Research Laboratory and is published by permission of the Director.

Organic Group, Chemical Research Laboratory,
D.S.I.R., Teddington, Middlesex. [*Received, November 5th*, 1957.]

[39] Martin and Webb, cited by Cornforth, Hunter, and Popjak, *Biochem. J.*, 1953, **54**, 597.

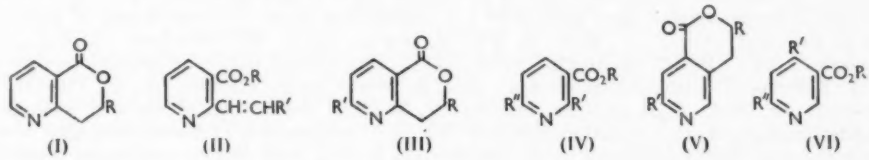
XUM

640. *Methylnicotinic Acids. Part II.*[1]

By E. Tittensor and D. G. Wibberley.

2-Methyl-, 2 : 6-dimethyl-, and 4 : 6-dimethyl-nicotinic acid and their ethyl esters have been condensed with benzaldehyde and *m*-nitrobenzaldehyde in the presence of acetic anhydride. In three cases lactones analogous to those reported in Part I were obtained; in others the products were mono- or di-styryl derivatives.

Condensation of aromatic aldehydes with 2-methyl-6-phenylnicotinic acid and its ethyl ester was shown in Part I [1] to give lactones (III; R = R′ = Ph). This work has been extended to condensation of 2-methyl-, 2 : 6-dimethyl-, and 4 : 6-dimethyl-nicotinic acid and their ethyl esters in the hope that other lactones could be prepared.



(I) (II) (III) (IV) (V) (VI)

Condensations were carried out with benzaldehyde or *m*-nitrobenzaldehyde and with acetic anhydride as catalyst, the intermediate 2- or 4-(2-hydroxyphenethyl)nicotinic acids not being isolated. 2-Methylnicotinic acid, or its ethyl ester, with benzaldehyde yielded 2-(2-hydroxyphenethyl)nicotinic lactone (I; R = Ph) which gave a positive hydroxamic acid test and was recovered unchanged after attempted ozonolysis. With *m*-nitrobenzaldehyde, however, the only product isolated was 2-3′-nitrostyrylnicotinic acid (II; R = H, R′ = $NO_2 \cdot C_6H_4$). This gave a negative hydroxamic acid test and on ozonolysis in ethyl acetate yielded an ozonide which was decomposed by aqueous silver nitrate to quinolinic acid. Where only one molecule of aldehyde condensed with the dimethylnicotinic acids or esters the 6-position was always attacked first. Thus 2 : 6-dimethylnicotinic acid yielded 2-methyl-6-styrylnicotinic acid (IV; R = H, R′ = Me, R″ = Ph·CH:CH) with benzaldehyde, 2-methyl-6-3′-nitrostyrylnicotinic acid (IV; R = H, R′ = Me, R″ = $NO_2 \cdot C_6H_4 \cdot$CH:CH) with *m*-nitrobenzaldehyde, and its ethyl ester the corresponding esters; 4 : 6-dimethylnicotinic acid gave the four analogous 4 : 6-compounds. All these styryl derivatives showed typical olefinic reactions. Their orientation was determined by ozonolysis: the acids gave 6-methylpyridine-2 : 5-dicarboxylic acid which was immediately decarboxylated, to give 2-methylnicotinic acid. Ethyl 4-methyl-6-styryl- and -6-3′-nitrostyryl-nicotinate gave 5-ethoxycarbonyl-4-methylpyridine-2-carboxylic acid, which showed the characteristic deep red coloration of a 2-carboxylic acid with ferrous sulphate solution and was readily decarboxylated to ethyl 4-methylnicotinate. When two molecules of benzaldehyde condensed with 2 : 6-dimethylnicotinic acid or its ethyl ester only 2-(2-hydroxyphenethyl)-6-styrylnicotinic lactone (III; R = Ph; R′ = Ph·CH:CH) was isolated, but with *m*-nitrobenzaldehyde 2-(2-hydroxy-3′-nitrophenethyl)-6-3′-nitrostyrylnicotinic lactone (III; R = R′ = $NO_2 \cdot C_6H_4 \cdot$CH:CH) was obtained from condensation with the ethyl ester, and 2 : 6-di-3′-nitrostyrylnicotinic acid (IV; R = H, R′ = R″ = $NO_2 \cdot C_6H_4 \cdot$CH:CH) from condensation with the acid. In condensation of two molecules of aldehyde with 4 : 6-dimethylnicotinic acid, the only products obtained were 4 : 6-distyrylnicotinic acid (VI; R = H, R′ = R″ = Ph·CH:CH) with benzaldehyde, and the 3′-nitrostyryl analogue with *m*-nitrobenzaldehyde. No lactone (V) was obtained in any condensation from 4 : 6-dimethylnicotinic acid or its ethyl ester.

[1] Part I, Tittensor and Wibberley, *J.*, 1956, 1778.

Experimental

2-(2-Hydroxyphenethyl)nicotinic Lactone.—Ethyl 2-methylnicotinate [2] (5·5 g.), benzaldehyde (4·8 g.), and acetic anhydride (3·1 c.c.) were refluxed for 14 hr. The resultant brown oil was triturated with 2N-hydrochloric acid to give a sticky solid which on crystallisation from ethanol gave *2-(2-hydroxyphenethyl)nicotinic lactone hydrochloride* (1·5 g.), m. p. 183—184° (Found: C, 59·7; H, 5·2; N, 5·3; Cl, 12·85. $C_{14}H_{12}O_2NCl,H_2O$ requires C, 60·1; H, 5·0; N, 5·0; Cl, 12·7%). The hydrochloride (0·17 g.) was suspended in water (4·0 c.c.), the suspension made alkaline with ammonia (*d* 0·88), boiled, and then cooled, and the *lactone* (0·11 g.) collected. Crystallisation from ethanol gave needles, m. p. 142—143° (Found: C, 74·4; H, 5·1; N, 6·3. $C_{14}H_{11}O_2N$ requires C, 74·6; H, 4·9; N, 6·2%). Basification of the acid layer yielded unchanged ethyl 2-methylnicotinate (1·2 g.).

The same lactone hydrochloride was isolated in 31% yield after condensation of 2-methylnicotinic acid.

2 : 3′-Nitrostyrylnicotinic Acid.—Similar condensation of ethyl 2-methylnicotinate (1·65 g.) with *m*-nitrobenzaldehyde (1·81 g.) in the presence of acetic anhydride (0·93 c.c.) (10 hr. reflux) yielded *2-3′-nitrostyrylnicotinic acid* (0·99 g.), crystallising from 2-ethoxyethanol in prisms, m. p. 230—232° [Found: C, 61·9; H, 3·8; N, 10·4%; equiv., 263 (titration). $C_{14}H_{10}O_4N_2$ requires C, 62·2; H, 3·7; N, 10·4%; equiv., 270]. Bromination in carbon tetrachloride gave *2-(1 : 2-dibromo-3′-nitrophenethyl)nicotinic acid* in prisms (from ethanol), m. p. 176—177° (Found: Br, 36·6. $C_{14}H_{10}O_4N_2Br_2$ requires Br, 37·2%). Basification of the acid washings yielded unchanged ethyl 2-methylnicotinate (0·3 g.). Condensation of 2-methylnicotinic acid gave the same styryl derivative as the sole product in 54% yield, but no unchanged starting material.

2-(2-Hydroxyphenethyl)-6-styrylnicotinic Lactone.—Ethyl 2 : 6-dimethylnicotinate [3] (2·8 g.) and benzaldehyde (2·4 g.) in acetic anhydride (1·4 c.c.) (10 hr. reflux) yielded the *lactone* (0·4 g.) in needles (from ethyl acetate), m. p. 200—201° (Found: C, 81·0; H, 5·2; N, 4·5. $C_{22}H_{17}O_2N$ requires C, 80·7; H, 5·2; N, 4·3%). *6-(1 : 2-Dibromophenethyl)-2-(2-hydroxyphenethyl)-nicotinic lactone* was obtained, by bromination of the lactone, in pale yellow needles, m. p. 236—238° (from 2-ethoxyethanol) (Found: N, 3·3; Br, 32·2. $C_{22}H_{17}O_2NBr_2$ requires N, 2·9; Br, 32·8%).

Ethyl 2-Methyl-6-styrylnicotinate.—Concentration of the alcoholic mother-liquors remaining after isolation of 2-(2-hydroxyphenethyl)-6-styrylnicotinic lactone yielded *ethyl 2-methyl-6-styrylnicotinate hydrochloride* (1·07 g.), needles (from 2-ethoxyethanol), m. p. 222—223° (decomp.) (Found: C, 67·25; H, 6·1; N, 5·0; Cl, 11·7. $C_{17}H_{18}O_2NCl$ requires C, 67·2; H, 5·9; N, 4·6; Cl, 11·7%). This with aqueous ammonia yielded *ethyl 2-methyl-6-styrylnicotinate*, which separated from ethanol in prisms, m. p. 68—69° (Found: C, 75·7; H, 6·2; N, 5·4. $C_{17}H_{17}O_2N$ requires C, 76·3; H, 6·35; N, 5·2%). Bromination in carbon tetrachloride gave *ethyl 6-(1 : 2-dibromophenethyl)-2-methylnicotinate*, needles (from ethanol), m. p. 138—139° (Found: N, 3·1; Br, 37·5. $C_{17}H_{17}O_2NBr_2$ requires N, 3·3; Br, 37·5%).

2 : 6-Dimethylnicotinic Acid.—Ethyl 2 : 6-dimethylnicotinate (5 g.) and 6·5N-sodium hydroxide (15·3 c.c.) were refluxed for 2 hr. The cooled solution was adjusted to pH 4·5 with 5N-hydrochloric acid and evaporated to dryness. The residue was extracted with ethanol, and the extract concentrated to give the *acid* (2·2 g.) which separated from ethanol in prisms, m. p. 170—171° (Found: C, 63·9; H, 6·1; N, 9·5. $C_8H_9O_2N$ requires C, 63·6; H, 6·0; N, 9·3%). Weiss [4] gives m. p. 160° for a hemihydrate.

2-Methyl-6-styrylnicotinic Acid.—(*a*) 2 : 6-Dimethylnicotinic acid (2·0 g.) and benzaldehyde (1·6 c.c.) in acetic anhydride (1·3 c.c.) (10 hr. reflux) gave a first crop of 2-(2-hydroxyphenethyl)-6-styrylnicotinic lactone (0·63 g.), m. p. and mixed m. p. 200—201°. *2-Methyl-6-styrylnicotinic acid* (0·66 g.) was isolated from the methanolic mother-liquors and recrystallised from ethyl acetate as plates, m. p. 192—194° (Found: C, 75·0; H, 5·6; N, 6·05%; equiv., 236. $C_{15}H_{13}O_2N$ requires C, 75·3; H, 5·4; N, 5·9%; equiv., 239).

(*b*) Ethyl 2-methyl-6-styrylnicotinate (0·43 g.) and 5N-sodium hydroxide (10 c.c.) were refluxed for 1 hr. The cooled solution was neutralised with acetic acid to give 2-methyl-6-styrylnicotinic acid (0·34 g.), m. p. and mixed m. p. 192—193° (from ethanol).

[2] Tsuda, Satch, Ikekawa, and Mishima, *J. Org. Chem.*, 1956, **21**, 800.
[3] Rabe, *Ber.*, 1912, **45**, 2120.
[4] Weiss, *Ber.*, 1886, **19**, 1308.

XUM

2-(2-*Hydroxy*-3′-*nitrophenethyl*)-6-3′-*nitrostyrylnicotinic Lactone*.—Ethyl 2 : 6-dimethylnicotinate (3·6 g.) and *m*-nitrobenzaldehyde (9·0 g.) in acetic anhydride (1·86 c.c.) (14 hr. reflux) gave the crude lactone (3·0 g.; m. p. 196—210°), which separated from acetic acid in pale yellow prisms, m. p. 230—232° [Found: C, 63·2; H, 3·8; N, 9·7%; equiv., 425 (hydrolysis). $C_{22}H_{15}O_6N_3$ requires C, 63·3; H, 3·6; N, 10·1%; equiv., 417].

Ethyl 2-*Methyl*-6-3′-*nitrostyrylnicotinate Hydrochloride*.—Repetition of the last experiment with less *m*-nitrobenzaldehyde (3·6 g.) and refluxing for 10 hr. yielded, after trituration with 2N-hydrochloric acid, *ethyl* 2-*methyl*-6-3′-*nitrostyrylnicotinate hydrochloride* (2·04 g.), m. p. (from 2-ethoxyethanol) 234—235° (Found: C, 58·3; H, 4·9; N, 8·2; Cl, 10·3. $C_{17}H_{17}O_4N_2Cl$ requires C, 58·4; H, 4·9; N, 8·0; Cl, 10·2%).

2-*Methyl*-6-3′-*nitrostyrylnicotinic Acid*.—(*a*) 2 : 6-Dimethylnicotinic acid (1·5 g.), *m*-nitrobenzaldehyde (1·8 g.), acetic anhydride (0·93 c.c.), and nitrobenzene (15 c.c.) were refluxed for 6·5 hr. The clear brown solution was cooled to give 2-*methyl*-6-3′-*nitrostyrylnicotinic acid* (1·2 g.), m. p. 230—232°. Recrystallisation from 2-ethoxyethanol gave cream needles, m. p. 238—239° (Found: C, 63·3; H, 4·0; N, 10·3%; equiv., 282. $C_{15}H_{12}O_4N_2$ requires C, 63·4; H, 4·2; N, 9·8%; equiv., 284).

(*b*) Ethyl 2-methyl-6-3′-nitrostyrylnicotinate hydrochloride (0·9 g.) and 3N-sodium hydroxide (30 c.c.) were refluxed for 2 hr. The mixture was diluted to 100 c.c. to give a clear solution. Hydrochloric acid was added to adjust to pH 5·0 and the mixture left for 2 hr. at 0°, to yield 2-methyl-6-3′-nitrostyrylnicotinic acid (0·47 g.), m. p. 227—230°, and on recrystallisation from 2-ethoxyethanol, m. p. and mixed m. p. 238—239°.

2 : 6-*Di*-3′-*nitrostyrylnicotinic Acid*.—2 : 6-Dimethylnicotinic acid (0·71 g.) and *m*-nitrobenzaldehyde (2·1 g.) in acetic anhydride (0·6 c.c.) and nitrobenzene (15 c.c.) yielded the *distyryl acid* (0·71 g.) in pale yellow prisms (from 2-ethoxyethanol), m. p. 228—230° (Found: C, 62·9; H, 3·9; N, 10·3%; equiv., 406. $C_{22}H_{15}O_6N_3$ requires C, 63·3; H, 3·6; N, 10·1%; equiv., 417).

4 : 6-*Dimethylnicotinonitrile*.—2-Chloro-4 : 6-dimethylnicotinonitrile [5] (35 g.), granulated tin (35 g.), concentrated hydrochloric acid (280 c.c.), and water (370 c.c.) were heated on the water-bath for 8 hr. The clear solution was made alkaline with sodium hydroxide, and the mixture extracted with chloroform. The extract was dried and distilled and the residual damp solid recrystallised directly from methanol, to give the *nitrile* (23·1 g.) in prisms, m. p. 54—56°. Recrystallisation from methanol raised the m. p. to 56—57° (Found: C, 71·9; H, 6·0; N, 20·7. $C_8H_8N_2$ requires C, 72·7; H, 6·05; N, 21·2%).

4 : 6-*Dimethylnicotinic Acid*.—2 : 6-Dimethylnicotinonitrile (15 g.) and 5N-potassium hydroxide were refluxed for 2 hr. The solution was acidified with concentrated hydrochloric acid, then concentrated *in vacuo*, and the dry residue extracted with ethanol (3 × 40 c.c.). The alcoholic extract was distilled, to leave 18·6 g., m. p. 247—253° (decomp.). A portion was recrystallised directly from ethanol to give 4 : 6-*dimethylnicotinic acid hydrochloride*, m. p. 257—259° (decomp.) (Found: C, 50·7; H, 5·3; N, 7·1. $C_8H_{10}O_2NCl$ requires C, 51·2; H, 5·3; N, 7·5%).

The remainder of the hydrochloride (17·4 g.) was stirred with the calculated amount of N-sodium hydroxide, and the solution concentrated on the water-bath *in vacuo*. The dry residue was extracted with boiling ethanol (3 × 40 c.c.), and the extract concentrated to 40 c.c. and cooled, to give the free *acid* in prisms, m. p. 193—194° (Found: C, 63·0; H, 6·1; N, 8·8. $C_8H_9O_2N$ requires C, 63·6; H, 6·0; N, 9·3%).

Ethyl 4 : 6-*Dimethylnicotinate*.—4 : 6-Dimethylnicotinic acid (5·0 g.), absolute ethanol (100 c.c.), and concentrated sulphuric acid (4 c.c.) were refluxed for 16 hr. The ethanol was removed by distillation from a water-bath. Water (100 c.c.) was added, the solution made alkaline with sodium hydroxide solution, and the liberated oil extracted with chloroform. The extract was dried and the chloroform distilled, to leave the *ester* (3·2 g.) (Found: N, 7·5. $C_{10}H_{13}O_2N$ requires N, 7·8%).

Ethyl 4-*Methyl*-6-*styrylnicotinate Hydrochloride*.—Ethyl 4 : 6-dimethylnicotinate (1·2 g.) and benzaldehyde (0·85 g.) in acetic anhydride (0·62 c.c.) (12 hr. reflux) gave the hydrochloride (1·3 g.), separating in cream needles (from ethanol), m. p. 203—204° (Found: C, 66·8; H, 6·3; N, 4·8; Cl, 11·5%; equiv., 314. $C_{17}H_{18}O_2NCl$ requires C, 67·2; H, 5·9; N, 4·6; Cl, 11·7%; equiv., 303·5). Condensation with excess of benzaldehyde gave the same compound as the sole product.

4-*Methyl*-6-*styrylnicotinic Acid*.—(*a*) 4 : 6-Dimethylnicotinic acid (3·0 g.) and benzaldehyde

[5] Mariella and Leech, *J. Amer. Chem. Soc.*, 1949, **71**, 332.

XUM

(2·54 g.) in acetic anhydride (1·86 c.c.) (11·5 hr. reflux) yielded the pale yellow *hydrochloride* (2·45 g.), m. p. 249—251° on recrystallisation from 2-ethoxyethanol (Found: C, 61·0; H, 5·7; N, 4·9; Cl, 12·1; H_2O, 7·0. $C_{15}H_{14}O_2NCl,H_2O$ requires C, 61·3; H, 5·45; N, 4·8; Cl, 12·1; H_2O, 6·1%).

(*b*) Ethyl 4-methyl-6-styrylnicotinate hydrochloride (0·1 g.), potassium hydroxide (1·0 g.), and water (3·0 c.c.) were refluxed for 2 hr. The cooled solution was acidified with concentrated hydrochloric acid to give the hydrochloride, m. p. 246—249° alone and 248—250° with the product obtained in (*a*). The hydrochloride (0·5 g.) was dissolved in aqueous ammonia and the pH of the solution adjusted to 5·0 with acetic acid. The liberated *4-methyl-6-styrylnicotinic acid* (0·32 g.) was collected and recrystallised from methanol, to give needles, m. p. 215—216° (Found: C, 74·8; H, 5·5; N, 6·0. $C_{15}H_{13}O_2N$ requires C, 75·3; H, 5·4; N, 5·9%).

4 : 6-*Distyrylnicotinic Acid.*—4 : 6-Dimethylnicotinic acid (2·0 g.) and benzaldehyde (5·1 g.) in acetic anhydride (1·28 c.c.) (12 hr. reflux) gave the *distyryl acid* (1·3 g.) in needles (from 2-ethoxyethanol), m. p. 233—234° (Found: C, 80·4; H, 5·1; N, 4·6. $C_{22}H_{17}O_2N$ requires C, 80·7; H, 5·2; N, 4·3%).

Pyridine-2 : 4 : 5-tricarboxylic Acid.—A solution of 4 : 6-distyrylnicotinic acid (0·1 g.) in ethyl acetate (20 c.c.) was treated with ozonised oxygen for 40 min. The solution was evaporated at room temperature and the ozonide decomposed by boiling dilute silver nitrate solution. The solid was collected and crystallised from methanol, to give the acid (0·04 g.) as the *hemihydrate*, m. p. 230—232° (decomp.) (Found: C, 43·1; H, 3·1; N, 6·5. $C_8H_5O_6N,\frac{1}{2}H_2O$ requires C, 43·5; H, 2·7; N, 6·4%). Mumm and Hüneke [6] give m. p. 243° for the dihydrate. The acid, in dilute acetic acid, gave a strong red-brown colour with ferrous sulphate.

4 : 6-*Di-3′-nitrostyrylnicotinic Acid.*—4 : 6-Dimethylnicotinic acid (1·0 g.), *m*-nitrobenzaldehyde (3·6 g.), acetic anhydride (0·7 c.c.), and nitrobenzene (20 c.c.) were refluxed for 12 hr. The mixture was diluted with ether, to give the *product* (1·9), m. p. >330°, insoluble in common solvents. It was boiled with 2-ethoxyethanol, the hot mixture filtered, and the insoluble solid dried and analysed directly (Found: C, 63·0; H, 3·8; N, 10·1. $C_{22}H_{15}O_6N_3$ requires C, 63·3; H, 3·6; N, 10·1%). The acid gave a negative hydroxamic acid test. The same acid was also isolated in 90% yield by reaction of the ethyl ester with *m*-nitrobenzaldehyde (3·0 mol.).

Ethyl 4-Methyl-6-3′-nitrostyrylnicotinate.—Ethyl 4 : 6-dimethylnicotinate (1·5 g.) and *m*-nitrobenzaldehyde (1·5 g.) in acetic anhydride (0·77 c.c.) (3 hr. reflux) gave a crude product (1·9 g.), m. p. 190—>330°. The product was boiled with 2-ethoxyethanol, and the hot mixture filtered, to leave 4 : 6-di-3′-nitrostyrylnicotinic acid (0·48 g.), m. p. >330°. The filtrate, on cooling, yielded *ethyl 4-methyl-6-3′-nitrostyrylnicotinate hydrochloride* (1·15 g.) in prisms (from 2-ethoxyethanol), m. p. 211—212° (Found: C, 58·5; H, 4·7; N, 8·0%; equiv., 362. $C_{17}H_{17}O_4N_2Cl$ requires C, 58·4; H, 4·9; N, 8·0%; equiv., 348·5). Treatment with aqueous ammonia gave *ethyl 4-methyl-6-3′-nitrostyrylnicotinate* in prisms (from ethanol), m. p. 130—131° (Found: C, 65·6; H, 4·9; N, 9·3. $C_{17}H_{16}O_4N_2$ requires C, 65·3; H, 5·1; N, 9·0%).

4-Methyl-6-3′-nitrostyrylnicotinic Acid.—(*a*) 4 : 6-Dimethylnicotinic acid (3·0 g.) and *m*-nitrobenzaldehyde (3·6 g.) in acetic anhydride (1·85 c.c.) (11 hr. reflux) yielded *4-methyl-6-3′-nitrostyrylnicotinic acid* (5·9 g.), m. p. 298—300° (from nitrobenzene) (Found: C, 62·8; H, 4·1; N, 10·0. $C_{15}H_{13}O_2N$ requires C, 63·4; H, 4·2; N, 9·8%).

(*b*) The same acid, m. p. 295—297° alone and 297—299° when mixed with the product from (*a*), was obtained by hydrolysis of ethyl 4-methyl-6-3′-nitrostyrylnicotinate hydrochloride with 6N-potassium hydroxide.

NOTTINGHAM AND DISTRICT TECHNICAL COLLEGE.
HUDDERSFIELD COLLEGE OF TECHNOLOGY.

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[6] Mumm and Hüneke, *Ber.*, 1918, **51**, 150.

641. *Infrared Studies of Heterocyclic Compounds. Part III.*[1] *3-Monosubstituted Pyridines.*

By A. R. Katritzky, A. R. Hands, and R. A. Jones.

The positions and intensities of eleven characteristic bands are recorded and discussed for twenty-seven 3-substituted pyridines.

Following our work on 2-[1] and 4-substituted pyridines,[2] we now report spectra for some 3-analogues. Cook and Church[3] investigated the spectra of 3-picoline (which has also been studied in detail[4]) and five nicotine derivatives containing a 3-substituted pyridine ring (as liquid films) and indicated that characteristic bands were at 1605—1585, 1587—1568, 1486—1475, 1427—1416, 1383—1377, 1318—1312, 1253—1239, 1196—1180, 1131—1117, 1034—1021, 810—789, and 715—712 cm.$^{-1}$; the fifth of these was stated to be " of variable intensity," but otherwise no indication of intensities was given. Shindo[5] correlated the spectra of thirteen 3-substituted pyridines (measured in Nujol, CS_2, CCl_4, or chloroform) and found characteristic bands at 1202—1182 (vw-s), 1130—1114 (w-m), 1016—1030 (m-s), 820—770 (m-s) and 730—690 cm.$^{-1}$ (vs). He also indicated that in general pyridines showed two bands between 1630 and 1560 cm.$^{-1}$ and that, in those 3-substituted pyridines with electron-donor substituents, the band of lower frequency was the stronger of the pair, but that the reverse was true of 3-pyridines with electron-acceptor substituents.*

In the present work, for reasons already given,[6] the spectra were all measured for 0·2M-solutions in chloroform in a 0·117 mm. cell, and apparent extinction coefficients recorded in place of " strong," " weak," etc. Eleven bands were found to be characteristic of the nucleus (see Table); they include all those found by the previous workers,[3,5] except those obscured by solvent (1240—1200 and below 805 cm.$^{-1}$), those at 1383—1377 cm.$^{-1}$ (apparently assigned to methyl absorption) and 1318—1312 cm.$^{-1}$. With very few exceptions, all other bands with $\varepsilon_A \geqslant 15$ were found to be characteristic of the substituent; they have already been published[6] for the methyl and the ethyl esters, the aldehyde, and the methyl ketone: in these seven compounds a total of 99 bands and 27 shoulders have been correlated and no band left unaccounted for.

The 3000 *cm.*$^{-1}$ *Region.*—The hydrogen-bonded chloroform CH stretching frequency[2] occurs (col. 1) at 3000—2940 [2980 ± 15] † cm.$^{-1}$; the intensity is (45—80) [(60 ± 13)] † except in the cyano- and nitro-compounds (probably less hydrogen-bonded because of low basicity) and in the ethyl and higher esters (overlapped by substituent absorption).

The 1650—1550 *cm.*$^{-1}$ *Region.*—Two bands occur. The first (col. 2) has a rather constant position at 1608—1584 [1595 ± 5] cm.$^{-1}$, but is of much higher intensity with both strong donor substituents [Nos. 1—7, (60—185)] and strong electron acceptor substituents [Nos. 17—27 (65—200)] than with substituents of a more neutral character [Nos. 8—16 (15—35)]. This intensity variation is similar to that in the corresponding band in 2-[7] and 4-substituted pyridine 1-oxides,[8] but different from those in the 2- and 4-pyridines;[1,2] this correlates well with the relative ease of electron-donor and -acceptor power of the rings (see discussion in ref. 8).

* In this paper, Shindo also discusses the spectra of twelve 2- and twelve 4-monosubstituted pyridines; as far as they go, his correlations are in good agreement with ours (refs. 1 and 2).

† Arithmetical means and standard deviations are given in square brackets, ε_A values in round brackets: see footnote in ref. 2.

[1] Part II, Katritzky and Hands, *J.*, 1958, 2202.
[2] Katritzky and Gardner, *J.*, 1958, 2198.
[3] Cook and Church, *J. Phys. Chem.*, 1957, **61**, 458.
[4] Long, Murfin, Hales, and Kynaston, *Trans. Faraday Soc.*, 1957, **53**, 1171 and references therein.
[5] Shindo, *Pharm. Bull.* (*Japan*), 1957, **5**, 472.
[6] Katritzky, Monro, Beard, Dearnaley, and Earl, *J.*, 1958, 2182.
[7] Katritzky and Hands, *J.*, 1958, 2195.
[8] Katritzky and Gardner, *J.*, 1958, 2192.

No.	Subst.	1 $CHCl_3$ νCH —	ε_A	2 A_1 νCC, CN 1611 ± 9s	ε_A	3 B_1 νCC, CN 1590 ± 7s	ε_A	4 B_1 νCC, CN 1499 ± 7vs	ε_A	5 A_1 νCC, CN 1447 ± 15m	ε_A	6 ? ? —	ε_A	7 B_1 βCH 1165 ± 6var	ε_A	8 A_1 βCH 1081 ± 10m	ε_A	9 B_1 βCH 1045 ± 7m	ε_A	10 A_1 ring 995 ± 5var	ε_A	11 B_2 γCH 782 ± 9vs	ε_A
		cm.$^{-1}$		cm.$^{-1}$		cm.$^{-1}$		cm.$^{-1}$		cm.$^{-1}$		cm.$^{-1}$		cm.$^{-1}$		cm.$^{-1}$		cm.$^{-1}$		cm.$^{-1}$		cm.$^{-1}$	
1	NHMe	2950	70	1595	185	1583 *	120	1484	95	1430 *	20	1191 *	45	1123	15	1100	25	1030 *	5	1008	20	—	
2	NH_2	2970	65	1590	95	(—)		1486	90	1442	125	1196 *	30	1130	30	1112	15	1042	15	1019	15	—	
3	OEt	2970	80	1589	60	1578	65	1482 *	50	1425	75	1183 *	30	1130 *	25	1100 *	35	(—)		1013 *	30	—	
4	NMe·COMe	2990	75	1590	70	1581 *	50	1480	145	1420 †	140	1190 *	30	(—)		1104	25	1040 *	20	1023	60	810 *	25
5	NMe·COPh	2960	50	(—)		1580	95	1488	150	1423 †	120	1175 *	35	(—)		1102 *	70	1044	20	1023 †	80	—	
6	NH·COMe	2970	70	1599	100	(—)		1480	225	1420 *	130	($CHCl_3$)		1124	20	1103	20	1047	15	1024	30	—	
7	NH·COPh	2990	60	1591	105	(—)		1481	290	1420	140	1190 *	40	1126	20	1098	25	1042	5	1026 †	45	—	
8	Me	2970	70	1600	15	1582	45	1479	55	1414	35	1188	20	1124	20	1102	20	1040	15	1029	55	—	
9	CH_2·CH_2·CO_2Et	2970	80	1600	20	1582	35	1479	55	1426	80	(—)		1124 *	40	1104 *	40	(—)		1028	75	—	
10	CH_2·CO_2Et	2970	85	1598	20	1580	40	1479	60	1426	90	1178 *	110	1117 *	35	(—)		1040 *	30	1027 †	175	—	
11	CH_2·OH	2940	75	1596	30	1580	45	1478	30	1424	60	1190 *	30	1122 *	15	1099	15	1042 *	50	(—)		—	
12	CH:CH·CO_2Et	2970	60	1592	35	1575	40	1477	50	1418	90	1186 *	200	1122	25	1111 *	20	1044	95	1025 †	110	(803	45)
13	Ph	2970	60	1584	20	(—)		1470	35	1408	85	($CHCl_3$)		1125	10	1100	10	1023 †	30	1006	60	808	20
14	C_6H_4·NO_2-*p*	2970	50	(—)		1572 †	25	1471	40	1428	45	1188 †	25	1128 *	15	1109 †	50	1025	25	1001	55	(804	50)
15	Cl	3000	45	1581 *	30	1573 *	30	1472	90	1419 1407 *	85 25	($CHCl_3$)		1120 *	35	1108 1093	125 35	—		1018	140	—	
16	Br	3000	50	1589 *	15	1576	25	1465 1440	50 30	1417	110	($CHCl_3$)		1117 *	15	1096 1086	70 50	1025 *	20	1009	110	—	
17	CN	3000	30	1590	65	1567	25	1471	25	1418	70	1184	20	1122	15	—		—		1025	60	(803	35)
18	CO_2Me	2970	45	1597	105	1580 *	30	—		1421	70	1188 †	50	1122 *	140	(—)		1036	20	1025	110	—	
19	CO_2Et	3000	95	1598	135	(—)		(—)		1422	85	1193 *	50	(—)		(—)		1039	55	1027 †	170	—	
20	CO_2Pr^n	2980	130	1595	135	1578 *	25	(—)		1419	85	1191 *	45	(—)		(—)		1037	25	1024 †	140	—	
21	CO_2Pr^i	3000	90	1600	135	1589 *	25	(—)		1424	75	1193 *	45	(—)		(—)		1037	15	1027 †	140	—	
22	CO_2Bu^n	2970	125	1594	120	1578 *	25	(—)		1420	75	1190 *	50	(—)		(—)		1035	20	1025 †	135	—	
23	CO_2Bu^i	2950	125	1599	120	1586 *	25	(—)		1420	65	1192 *	60	(—)		(—)		1037	20	1026 †	125	—	
24	CO_2Bu^s	2980	95	1597	100	1580 *	20	—		1420	50	1191 *	55	(—)		(—)		1037 *	15	1025 †	115	—	
25	CHO	2990	45	1595	200	1581 *	80	—		1428	50	(—)		1120 *	15	1109	20	1035 *	20	1025	55	—	
26	COMe	2970	45	1589	170	(—)		—		1419	105	1193 *	45	1118	35	(—)		1032 *	10	1023	80	808	30
27	NO_2	3000	25	1608	190	1580	75	1472	20	1428	55	1192	70	1114	20	1100	20	—		1021	70	820	50

Tentative assignments of symmetry and type of vibration, and the arithmetical mean and standard deviation for the corresponding band in *meta*-disubstituted benzenes (from Ref. 9), are given immediately below the column number.

* Shoulder. † Absorption considered to be the superimposition of two bands, — absence of absorption, (—) band masked by stronger absorption, ($CHCl_3$) band masked by solvent.

The second band (col. 3) occurs at 1582—1567 [1577 ± 5] cm.$^{-1}$ with intensity (25—75) [(45 ± 15)] (except in No. 5 where it is overlapped). This band often occurs only as a shoulder on the previous band, and sometimes instead of the two bands only one is observed, usually that at higher frequencies.

The 1500—1400 *cm.*$^{-1}$ *Region.*—Usually two bands are found. One (col. 4) occurs at 1486—1480 cm.$^{-1}$ with electron donor substituents (Nos. 1—7), at 1479—1477 cm.$^{-1}$ with electronically neutral substituents (Nos. 8—12), but is lowered to 1472—1465 cm.$^{-1}$ by aryl, halogen, and electron attracting-substituents. The intensity is very high for the amides (145—290) and moderate with other electron-donor and neutral substituents (Nos. 1—3, 8—16) (30—95) [(65 ± 20)]; the band is weak or absent in compounds with electron-attracting substituents (Nos. 17—27).

Another band (col. 5) is at 1428—1414 cm.$^{-1}$ [1421 ± 4], except for the amino-compounds at 1442 cm.$^{-1}$. The intensity is (35—140) [(80 ± 25)].

The 1200—990 *cm.*$^{-1}$ *Region.*—Five bands are found. The first (col. 6) occurs at the edge of the portion of the spectrum obscured by solvent (*i.e.*, 1240—1200 cm.$^{-1}$) and usually is seen only as a shoulder.

Another band (col. 7) occurs at 1130—1114 cm.$^{-1}$ (10—35) [1124 ± 5 cm.$^{-1}$ (20 ± 10)]; it is often hidden by, or seen as a shoulder on, substituent absorption.

The third band (col. 8) is absent for No. 17, otherwise it is at 1112—1096 cm.$^{-1}$ [1103 ± 5]. The intensity is (10—25) [(20 ± 5)], except for the halogeno-compounds (Nos. 15 and 16) which cause abnormally strong absorption in this region in other series.[1,2,7,8]

A weak band (col. 9) (absent in Nos. 15, 17, and 27) is found at 1047—1040 cm.$^{-1}$ with electron-donor and most neutral substituents (Nos. 1—12), at 1039—1035 cm.$^{-1}$ with electron-acceptor substituents (Nos. 18—26), but the frequency is lowered to *ca.* 1025 cm.$^{-1}$ with halogeno- and aryl substituents. The intensity is (5—25) [(20 ± 5)] except for Nos. 12 and 19 where the band is strongly overlapped by substituent absorption.

The final band in this region (col. 10) occurs at 1029—1021 cm.$^{-1}$ [1025 ± 2] except in the amino-, aryl- and halogeno-substituted compounds which all absorb at lower frequencies. The intensity is (15—140) [(65 ± 35)].

The 900—800 *cm.*$^{-1}$ *Region.*—For a few compounds a band (col. 11) occurs on the edge of the region hidden by solvent absorption below 805 cm.$^{-1}$.

Assignments.—Comparison with Randle and Whiffen's data [9] for *meta*-substituted benzenes suggests the assignments indicated at the head of the Table; the agreement is, however, not as good as for 2- and 4-substituted pyridines;[1,2] the bands at [964 ± 10 (w), 904 ± 13 (var) and 876 ± 10 cm.$^{-1}$ (vs)] appear to have no analogues in the 3-pyridines, and the assignment of the 3-pyridine band at *ca.* 1190 cm.$^{-1}$ is uncertain.

Experimental.—See ref. 2 for sources of specimens, and conditions for measurement of the spectra.

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THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.
THE CHEMICAL LABORATORY, CAMBRIDGE UNIVERSITY. [*Received, March* 31*st*, 1958.]

[9] Randle and Whiffen, Report on Conference on Molecular Spectroscopy, 1954, Inst. Petroleum, Paper No. 12, p. 111.

XUM

642. *The Effect of Conformation on the Rate of Unimolecular Solvolysis of Aralkyl Chlorides.*

By G. Baddeley, J. W. Rasburn, and R. Rose.

The rates of solvolysis of 1-chloroindane and 1-chlorotetralin and of their 2-methyl and 2 : 2-dimethyl derivatives in ethanol at several temperatures have been measured. The 2-methyl groups hinder solvolysis to nearly the same extent as do 2-methyl substituents in 1-phenylpropyl chloride. The similarity casts doubt on the correctness of our previous conclusion [1] that differences between the reactivities of the chlorides R·CHPhCl, where R is a primary, secondary, and tertiary alkyl group severally, are caused *mainly* by differences in steric hindrance of ionisation.

The rate of ethanolysis of 1-chloro-2-deuteroindane is 87% of that of 1-chloroindane.

Comparison of the ultraviolet absorption spectra of indan-1-one and tetral-1-one with those of their 2-methyl and 2 : 2-dimethyl derivatives shows that the 2-methyl groups, unlike the methyl groups of *tert.*-butyl phenyl ketone, do not hinder conjugation of the carbonyl group and the benzene ring.

The reactivity of the aralkyl chlorides R·CHPhCl towards solvolysis in 80% aqueous ethanol decreases in the order R = Me > Et > Pr^i > Bu^t and we have argued [1] that this is the order of increasing steric hindrance of ionisation of the chlorides. These compounds will prefer those conformations in which R, being a bulky group, avoids the plane of the benzene ring whereas R must lie in or near this plane in the benzyl cation if this is to have maximum resonance energy; thus ionisation of the chloride is hindered by the increase of steric interaction as R approaches the plane of the ring and by loss of resonance energy in the benzyl cation if this, for steric reasons, is not approximately planar. It was recognised at that time that other interpretations of the decrease in reactivity might invoke decrease in hyperconjugation in, and increase of steric hindrance of solvation of, the aralkyl cation in the above order, but these effects were largely discounted since they might be expected to apply also to the solvolysis of the alkyl chlorides R·CMe_2Cl and it was already known that the reactivity of these compounds is only little affected by change of R from primary to secondary to tertiary alkyl group. The comparatively high reactivity of 1-chloroindane and 1-chlorotetralin [2] was offered as further evidence for our argument: these compounds have nearly the same conformation of the carbon skeleton as is required for maximum resonance stabilisation in the transition state of the ionisation process and, not having to change conformation during reaction, are essentially free from steric hindrance of ionisation.

The present paper is concerned with the relative reactivities of 1-chloroindane and 1-chlorotetralin and their 2-methyl and 2 : 2-dimethyl derivatives (I and II; R = R′ = H; R = Me, R′ = H; R = R′ = Me). According to the above steric considerations, these replacements of a hydrogen atom by a methyl group should provide a steric hindrance of ionisation of the resulting chloride which is negligible or, in any case, small in comparison with that given by the corresponding replacements in 1-phenylpropyl chloride (III; R = R′ = H). This expectation finds support, if this is needed, in the comparison of the ultraviolet absorption spectra of the series of ketones (V) and (VI) with those of the series (VII) (see Table 1). It is seen that conjugation of a carbonyl group and a benzene ring in *tert.*-butyl phenyl ketone (VII; R = R′ = Me) is hindered whereas that in the 2 : 2-dimethyl derivatives of indan-1-one and tetral-1-one (V and VI respectively; R = R′ = Me) is not. The absorption spectra of the semicarbazones are given in the

[1] Baddeley, Chadwick, and Taylor, *J.*, 1954, 2405.
[2] Baddeley and Chadwick, *J.*, 1951, 368.

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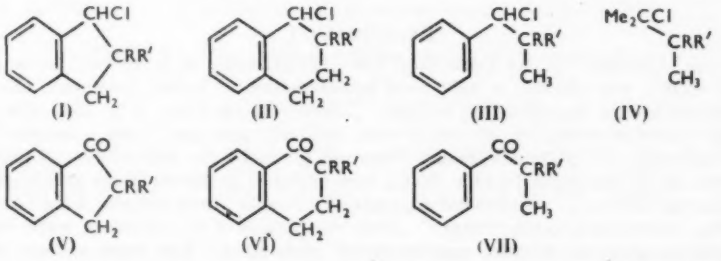
TABLE 1. *The ultraviolet absorption spectra of the ketones.*

	$\lambda_{max.}$ (Å)		ε	
Indan-1-one	2430	2880	12,650	3000
2-Methylindan-1-one	2450	2900	9,900	2100
2 : 2-Dimethylindan-1-one	2450	2920	11,450	2650
Tetral-1-one	2475	2900	11,550	1900
2-Methyltetral-1-one	2465	2900	9,600	1500
2 : 2-Dimethyltetral-1-one	2465	2880	10,900	1600
Ph·CO·R				
R = Et	2380	2770	11,450	880
R = Pr^{i}	2375	2770	11,500	850
R = Bu^{t}	2360	no max.	8,100	no max.

Experimental section. The semicarbazone of 2 : 2-dimethylindanone was difficult to prepare; that of 2 : 2-dimethyltetralone was not obtained. The kinetic data are assembled in Table 2, while in Table 3 the reactivities of the series of chlorides (I), (II), and (III)



are compared with one another and with those of the series of tertiary alkyl chlorides (IV). It is noteworthy that the 1-chloro-2-methyl derivatives of indane and tetralin are almost identical in their behaviour towards anhydrous ethanol.

TABLE 2. *Constants of the Arrhenius equation, $k = Ae^{-E/RT}$, for the formation of hydrogen chloride by ethanolysis of the chlorides.*

	10^4k_1 (min.$^{-1}$)					E (kcal. mole^{-1})	$10^{-13}A$ (min.$^{-1}$)
	0·0°	15·0°	25·0°	40·0°	50·0°		
1-Chloroindane	3·35	26·1	90·8	—	—	21·6	6·76
1-Chloro-2-methylindane	0·316	2·75	10·6	66·1	—	22·8	4·27
1-Chloro-2 : 2-dimethylindane	—	0·462	1·76	10·9	36·0	23·0	1·07
1-Chlorotetralin	0·521	5·01	19·7	132	—	23·2	17·4
1-Chloro-2-methyltetralin	—	2·51	9·6	58·9	174	22·9	4·68
1-Chloro-2 : 2-dimethyltetralin	—	—	1·78	13·8	52·5	26·4	324

TABLE 3. *Relative reactivities of the chlorides* (I) *and* (II) *in absolute ethanol and of the chlorides* (III) *and* (IV) *in* 80% *aqueous ethanol.*

	(I)		(II)		(III) [1]		(IV) *	
	log $k_{25°}$ (rel.)	E	log $k_{25°}$ (rel.)	E	log $k_{45°}$ (rel.)	E	log $k_{25°}$ (rel.)	E
R = R′ = H	2·93	21·6	2·31	23·2	2·67	20·7	2·25	21·0
R = Me, R′ = H	2·00	22·8	2·00	22·9	2·00	22·9	2·00	21·4
R = R′ = Me	1·22	23·0	1·27	26·4	0·57	25·4	2·13	21·4

* Brown, Davies, Dostrovsky, Evans, and Hughes, *Nature*, 1951, **167**, 987.

Contrary to expectation, the reactivities of the chlorides (I) and (II) decrease in the order R = R′ = H > R = Me, R′ = H > R = R′ = Me and to an extent which is similar to, if somewhat less than, that for the reactivities of the chlorides (III). The similarity casts doubt on our previous conclusion that differences between the reactivities

of the chlorides in series (III) are caused *mainly* by differences in steric hindrance of ionisation. The sequence of decreasing reactivity in the three series of aralkyl chlorides is also that of decreasing hyperconjugation in the corresponding series of aralkyl cations, but change in hyperconjugation does not usually provide differences in reactivity as large as those reported here. Further, change in hyperconjugation does not provide correspondingly large differences in reactivity between the members of the alkyl chlorides (IV). That hyperconjugation contributes to the ease of ionisation of 1-chloroindane is indicated by the data in Table 4: they show that replacement of hydrogen by deuterium atom at the 2-position effects a decrease of 13% in the rate of ionisation.

TABLE 4. *Comparison of the reactivities of* 1*-chloroindane and its* 2*-deutero-derivative in absolute ethanol.*

	$10^4k_{0\cdot0}$ (min.$^{-1}$)	$10^4k_{15\cdot0}$ (min.$^{-1}$)	$10^4k_{25\cdot0}$ (min.$^{-1}$)	E (kcal. mole^{-1})	$10^{-13}A$ (min.$^{-1}$)
1-Chloroindane	3·35	26·1	90·8	21·6	6·76
1-Chloro[2-^{2}H$_1$]indane	2·89	22·8	79·7	21·7	5·43
k_D/k_H	0·86	0·87	0·88	—	—

EXPERIMENTAL

Materials.—Ketones. Indan-1-one, b. p. 129—131°/12 mm., m. p. 40—41° (semicarbazone, m. p. 237—238°), was afforded in 94% yield by interaction of β-phenylpropionyl chloride and aluminium chloride in thiophen-free benzene. 2-Methylindan-1-one, b. p. 132—134°/18 mm., n_D^{20} 1·5430 (semicarbazone, m. p. 195°), was similarly prepared from α-methyl-β-phenylpropionyl chloride. 2 : 2-Dimethylindan-1-one was given by the methylation of indan-1-one. This ketone (20 g.) and methyl iodide (30 g.) were added to sodamide [from sodium (4·5 g.)] in liquid ammonia (200 c.c.). Additional amounts of sodamide (from sodium, 4·5 g.) and methyl iodide (30 g.) were added to the mixture. After evaporation of the ammonia, water was added to the residue, and the mixture was extracted with ether. The ether extract was dried (K_2CO_3) and the ether was evaporated. The residue was further methylated as described above and gave 2 : 2-dimethylindan-1-one (13·5 g.), b. p. 113—115°/13 mm., m. p. 43—44° (Found: C, 82·6; H, 7·3. Calc. for $C_{11}H_{12}O$: C, 82·5; H, 7·5%) [semicarbazone, m. p. 195—197° (Found: C, 66·5; H, 7·0; N, 19·2. Calc. for $C_{12}H_{15}ON_3$: C, 66·4; H, 6·9; N, 19·4%)]. Tetral-1-one, b. p. 122—124°/9 mm. (semicarbazone, m. p. 222—223°), and 2-methyltetral-1-one, b. p. 129—131°/11 mm., n_D^{20} 1·5516 [semicarbazone, m. p. 200—201° (Found: C, 66·4; H, 6·7; N, 19·4. Calc. for $C_{12}H_{15}ON_3$: C, 66·4; H, 6·9; N, 19·3%)], were prepared from γ-phenylbutyryl chloride and its α-methyl derivative respectively through the agency of aluminium chloride in thiophen-free benzene. 2 : 2-Dimethyltetral-1-one, b. p. 128—130°/13 mm., was afforded by the action of sulphuric acid (80% v/v) on γ-phenyl-αα-dimethylbutyric acid and did not give a semicarbazone.

Alcohols. These were obtained from the ketones by the action of lithium aluminium hydride and crystallised from light petroleum: indan-1-ol,[3] b. p. 119—120°/9 mm., m. p. 52—53°; *2-methylindan-1-ol*, b. p. 122—123°/15 mm., m. p. 78—79° (Found: C, 81·0; H, 8·2. $C_{10}H_{12}O$ requires C, 81·1; H, 8·1%) [*phenylurethane*, m. p. 89° (Found: C, 76·8; H, 6·4; N, 5·3. $C_{17}H_{17}O_2N$ requires C, 76·4; H, 6·4; N, 5·2%)]; 2 : 2-*dimethylindan-1-ol*, b. p. 138—140/°10 mm., m. p. 56—57° (Found: C, 81·1; H, 8·5. $C_{11}H_{14}O$ requires C, 81·5; H, 8·6%) [*phenylurethane*, m. p. 90—91° (Found: C, 77·0; H, 7·0; N, 5·0. $C_{18}H_{19}O_2N$ requires C, 76·8; H, 6·8; N, 5·0%)]; tetral-1-ol, b. p. 132—134°/12 mm., n_D^{20} 1·5672 (phenylurethane, m. p. 121°); *2-methyltetral-1-ol*, b. p. 138—140°/15 mm., m. p. 69—70° (Found: C, 81·8; H, 9·1. $C_{11}H_{14}O$ requires C, 81·5; H, 8·6%) [*phenylurethane*, m. p. 90—92° (Found: C, 77·5; H, 6·9; N, 5·1. $C_{18}H_{19}O_2N$ requires C, 76·9; H, 6·8; N, 5·0%)]; 2 : 2-*dimethyltetral-1-ol*, b. p. 136—138°/16 mm., m. p. 44·5—45·5° (Found: C, 81·7; H, 8·7. $C_{12}H_{16}O$ requires C, 81·8; H, 9·1%) [*phenylurethane*, m. p. 90—91° (Found: C, 77·2; H, 7·2; N, 5·0. $C_{19}H_{21}O_2N$ requires C, 77·3; H, 7·1; N, 4·7%)].

When required for solvolysis in absolute ethanol, the chlorides were obtained by the action of dry hydrogen chloride on the alcohols in light petroleum in the presence of calcium chloride. 1-Chloroindane, b. p. 90—92°/10 mm. (Found: Cl, 22·3. Calc. for C_9H_9Cl: Cl, 23·3%), was

[3] Weissgerber, *Ber.*, 1911, **44**, 1445.

also obtained by the method of Haworth, Lindley, and Woodcock.[4] It reacted with thiourea in dioxan and the product, with picric acid, gave 1-*indanylthiouronium picrate*, m. p. 158° (Found: C, 45·7; H, 3·7; N, 16·7. $C_{16}H_{15}O_7N_5S$ requires C, 45·6; H, 3·6; N, 16·6%). 1-*Chloro*[2-$^2H_1$]*indane*, b. p. 95—96°/12 mm. (Found: C, 70·5; H + D, 6·6; Cl, 22·9. C_9H_8DCl requires C, 70·4; H + D, 6·6; Cl, 23·1%), was given by interaction of dry deuterium chloride, prepared from benzoyl chloride and deuterium oxide (99·77%) as described by Brown and Groot,[5] and indene at −15° in a closed system, and was purified by repeated distillation under reduced pressure. It gave a *thiuronium picrate*, m. p. 158—158·5° (Found: C, 45·8; H + D, 3·7; N, 16·1. $C_{16}H_{14}DO_7N_5S$ requires C, 45·5; H + D, 3·8; N, 16·6%).

Ethanolysis of the Chlorides.—The ethanol was dried over magnesium ethoxide by the method of Lund and Bjerrum [6] and redistilled from magnesium ethoxide before each experiment. Ethanol (120—150 c.c.) in a flask (250 c.c.) fitted with ground-glass stopper was placed in a thermostat at the selected temperature. After an hour, the chloro-compound (0·25—0·4 c.c.) was quickly added by dropper-pipette, and the mixture was vigorously agitated. Samples (10 c.c.) were removed at selected times, run into dry acetone (40 c.c.) and titrated (lacmoid indicator) with ethanolic 0·01N-sodium ethoxide. Each determination was repeated several times; the average rate constants are listed in Tables 2 and 4. When the selected temperature was 50°, samples (10 c.c.) of the reaction mixture were heated in sealed tubes.

TABLE 5. *Ultraviolet absorption spectra of the semicarbazones.*

	$\lambda_{max.}$ (Å)				ε			
Indan-1-one	2700	2790	2975	3090	15,600	16,000	14,500	12,800
2-Methylindan-1-one	2700	2790	2970	3075	15,000	15,600	13,400	12,300
2 : 2-Dimethylindan-1-one	2720 *	2810	2975	3090 *	9,600 *	10,200	11,900	10,400 *
Tetral-1-one	2780	2850	—	—	18,000	17,900	—	—
2-Methyltetral-1-one	2800	2850	—	—	15,800	15,500	—	—

* Shoulder.

The ultraviolet absorption spectra of the ketones (see Table 1) and semicarbazones (Table 5) in hexane were measured with a Hilger Uvispek Photoelectric Spectrophotometer.

MANCHESTER COLLEGE OF SCIENCE AND TECHNOLOGY, MANCHESTER, 1.

[*Received, April 1st,* 1958.]

[4] Haworth, Lindley, and Woodcock, *J.*, 1947, 369.
[5] Brown and Groot, *J. Amer. Chem. Soc.*, 1942, **64**, 2223.
[6] Lund and Bjerrum, *Ber.*, 1931, **64**, 210.

643. *Relation between Hyperconjugation and Conformation. Part II. The Ethyl Alcoholysis of Some Homologues of Diphenylmethyl Chloride.*

By G. BADDELEY, S. VARMA, and (in part) M. GORDON.

The reactivities of the 4-alkyldiphenylmethyl (4-alkylbenzhydryl) chlorides R·CH_2·C_6H_4·CHPhCl, where R is H, Me, Et, Pr^i, and Bu^t, in dry ethyl alcohol are shown to decrease in this order. 3 : 5-Dimethyl-, 3 : 4 : 5-trimethyl-, 4-ethyl-3 : 5-dimethyl-, and 3 : 5-dimethyl-4-propyl-diphenylmethyl chloride have been prepared. Their reactivities in the ethanolysis reaction indicate that the hyperconjugative effect of the 4-ethyl and the 4-propyl group is not hindered by methyl groups in the 3- and 5-positions and, therefore, that in these instances hyperconjugation of a primary alkyl group is unaffected by torsional rotation of the group about the bond attaching it to benzene ring.

RATES of solvolysis decrease in the series 3 : 4-*cyclo*penteno- > 3 : 4-*cyclo*hexeno- > 3 : 4-*cyclo*hepteno-benzhydryl chloride and have been offered [1] as evidence for the view [2] that

[1] Part I, Baddeley and Gordon, *J.*, 1952, 2190; Arnold and Truett, *J. Amer. Chem. Soc.*, 1951, **73**, 5508.
[2] Baddeley, Chadwick, and Rawlinson, *Nature*, 1949, **164**, 833.

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the hyperconjugative release of electrons by a methylene group is a maximum when its hydrogen atoms are placed one on either side of the plane of the attached benzene ring and is hindered by forces which oppose this conformation. Several groups of workers have shown that primary alkyl groups CH_2R attached to an aromatic system provides a hyperconjugative release of electrons which decreases in the order R = H > Me > Et > Pr^i > Bu^t; this has been interpreted in terms of second-order hyperconjugation, partial suppression of hyperconjugation of the CH_2 group by the inductive effect of R, steric hindrance of solvation, and steric hindrance of hyperconjugation severally. The last interpretation is based on the assumption that hyperconjugation in the system Ar·CH_2R, like conjugation in ArOR, Ar·NHR, Ar·COR, etc., is a maximum when R is in the plane of the aromatic ring and diminishes progressively as the side-chain of which R is a part is rotated through an angle of 90°. It follows that non-bonding interaction of R and the ring, in the order R = Me < Et < Pr^i < Bu^t, will hinder hyperconjugation. The work reported in this paper was designed to check the validity of this interpretation and involves the following argument. Should the positions *ortho* to the CH_2R group be occupied by bulky substituents, steric hindrance of hyperconjugation should be nearly independent of the size of the alkyl group R, for R, even when only a methyl group, would avoid the plane of the ring. Thus in the presence of bulky *ortho*-substituents the usual sequence of hyperconjugative effects, R = H > Me > Et > Pr^i > Bu^t, should become R = H ≫ Me = Et = Pr^i = Bu^t. The former is conveniently illustrated by the solvolysis of the 4-alkylbenzhydryl chlorides R·CH_2·C_6H_4·CHPhCl; our data are assembled in Table 1. Since this work was completed Shiner and Verbanic [3] have reported the preparation of these chlorides and their rates of solvolysis in aqueous ethanol and aqueous acetone.

TABLE 1. *Arrhenius parameters for the solvolysis of 4-alkyldiphenylmethyl chlorides in dry ethyl alcohol.*

4-Substituent	$10^5k_{0\cdot0}$ (sec.$^{-1}$)	$10^5k_{20\cdot0}$ (sec.$^{-1}$)	$10^5k_{25\cdot0}$ (sec.$^{-1}$)	E (kcal. mole^{-1})	$10^{-11}A$ (sec.$^{-1}$)
None	0·188	2·88	5·37	21·8	4·47
Methyl (R = H)	6·12	70·8	123	19·5	2·14
Ethyl (R = Me)	5·50	67·6	120	20·0	5·13
Propyl (R = Et)	4·70	58·9	105	20·2	5·89
2-Methylpropyl	4·41	56·2	100	20·3	6·46
2 : 2-Dimethylpropyl	3·93	51·8	93·3	20·6	10·0

TABLE 2. *Arrhenius parameters for the solvolysis of 4-alkyl-3 : 5-dimethyldiphenylmethyl chlorides in dry ethyl alcohol.*

4-Substituent	$10^5k_{0\cdot0}$ (sec.$^{-1}$)	$10^5k_{20\cdot0}$ (sec.$^{-1}$)	E (kcal. mole^{-1})	$10^{-11}A$ (sec.$^{-1}$)
None	0·810	11·4	21·1	5·5
Methyl (R = H)	27·3	286	18·8	2·5
Ethyl (R = Me)	25·1	273	19·1	3·8
Propyl (R = Et)	22·8	255	19·3	5·4

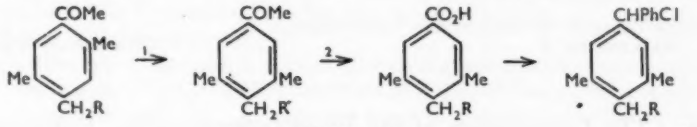
TABLE 3. *Comparison of the rate constants and activation energies for ethanolysis of the 4-alkyldiphenylmethyl chlorides with those for ethanolysis of the 3 : 5-dimethyl derivatives.*

4-Substituent		H	Me (R = H)	Et (R = Me)	Pr (R = Et)
3 : 5-Substituents:					
H	$k_{20\cdot0}$ (rel.)	1·00	24·6	23·5	20·5
Me	$k_{20\cdot0}$ (rel.)	1·00	25·1	24·0	22·4
H	E (kcal. mole^{-1})	21·8	19·5	20·0	20·2
Me	E (kcal. mole^{-1})	21·1	18·8	19·1	19·3
	ΔE	0·7	0·7	0·9	0·9

Our present purpose would be served if the reactivities of these chlorides could be compared with those of their 3 : 5-dimethyl derivatives (I). These compounds are accessible by the formulated route only when the 4-alkyl group is methyl, ethyl, or *n*-propyl

[3] Shiner and Verbanic, *J. Amer. Chem. Soc.*, 1957, **79**, 369.

and the comparison has been confined to these instances; the Arrhenius constants for their solvolysis in dry ethanol are listed in Table 2. In Table 3 the relative reactivities of the 4-alkylbenzhydryl chlorides are compared with, and shown to be similar to, those of their 3 : 5-dimethyl derivatives. The comparison, therefore, does not provide evidence for the view that the hyperconjugative effect of primary alkyl group is affected by torsional rotation of the group about the bond attaching it to benzene ring.



Reagents: 1, $AlCl_3$. 2, NaOCl. (I)

Experimental

Materials.—**3 : 5-*Dimethyldiphenylmethyl chloride*.** 3 : 5-Dimethylbenzophenone,[4] m. p. 69°, with lithium aluminium hydride gave 3 : 5-dimethyldiphenylmethanol (73%), b. p. 161—163°/1·0 mm., radiating needles, m. p. 50—51° (from light petroleum), which has previously been obtained [5] only as a liquid (Found: C, 84·5; H, 7·3. Calc. for $C_{15}H_{16}O$: C, 84·9; H, 7·6%). The alcohol with hydrogen chloride [6] gave **3 : 5-*dimethyldiphenylmethyl chloride*,** b. p. 143°/0·1 mm. (Found: Cl, 15·4. $C_{15}H_{15}Cl$ requires Cl, 15·6%).

3 : 4 : 5-*Trimethyldiphenylmethyl chloride*. Hypochlorite oxidation of 3 : 4 : 5-trimethylacetophenone [7] gave the corresponding benzoic acid,[8] m. p. 214°; Friedel–Crafts interaction at 70° of its *chloride*, b. p. 140°/15 mm. (Found: Cl, 19·4. $C_{16}H_{17}OCl$ requires Cl, 19·45%) (obtained by the action of thionyl chloride), and benzene gave **3 : 4 : 5-*trimethylbenzophenone*,** b. p. 198—200°/14 mm., $n_D^{17\cdot5}$ 1·6002 (Found: C, 85·5; H, 7·3. $C_{16}H_{16}O$ requires C, 85·7; H, 7·1%). Use of lithium aluminium hydride gave **3 : 4 : 5-*trimethyldiphenylmethanol*** as prisms, m. p. 81—82° (from light petroleum) (Found: C, 84·7; H, 7·9. $C_{16}H_{18}O$ requires C, 85·0; H, 8·0%), from which the required *chloride*, b. p. 154—155°/0·06 mm. (Found: Cl, 14·4. $C_{16}H_{17}Cl$ requires Cl, 14·5%), was obtained.

4-*Ethyl*-3 : 5-*dimethyldiphenylmethyl chloride*, b. p. 162°/0·1 mm. (Found: Cl, 13·8. $C_{17}H_{19}Cl$ requires Cl, 13·7%), was similarly obtained from 4-ethyl-3 : 5-dimethylacetophenone.[7] **2-*Ethyl*-3 : 5-*dimethylbenzoic acid*** separated from benzene in plates, m. p. 178—179° (Found: C, 74·6; H, 7·6. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·8%), and its *chloride*, b. p. 152—154°/19 mm. (Found: Cl, 18·0. $C_{11}H_{13}OCl$ requires Cl, 18·1%), gave **4-*ethyl*-3 : 5-*dimethylbenzophenone*,** b. p. 149—152°/0·12 mm. (Found: C, 85·2; H, 7·4. $C_{17}H_{18}O$ requires C, 85·7; H, 7·6%). **4-*Ethyl*-3 : 5-*dimethyldiphenylmethanol*** separated from light petroleum in needles, m. p. 75—76° (Found: C, 84·7; H, 8·1. $C_{17}H_{20}O$ requires C, 85·0; H, 8·3%), and gave the required *chloride*, b. p. 162°/0·1 mm. (Found: Cl, 13·8. $C_{17}H_{19}Cl$ requires Cl, 13·7%).

3 : 5-*Dimethyl*-4-n-*propyldiphenylmethyl chloride*, b. p. 165—167°/0·4 mm. (Found: Cl, 12·8. $C_{18}H_{21}Cl$ requires Cl, 13·0%), was prepared from 3 : 5-dimethyl-4-*n*-propylacetophenone.[7] **3 : 5-*Dimethyl*-4-n-*propylbenzoic acid*,** needles, m. p. 105° (Found: C, 74·9; H, 8·1. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%), its *chloride*, b. p. 153—153·5°/15 mm. (Found: Cl, 16·7. $C_{12}H_{15}OCl$ requires Cl, 16·9%), **3 : 5-*dimethyl*-4-n-*propylbenzophenone*,** b. p. 217—218°/18 mm. (Found: C, 85·4; H, 7·9. $C_{18}H_{20}O$ requires C, 85·7; H, 7·9%), and **3 : 5-*dimethyl*-4-n-*propyldiphenylmethanol*,** b. p. 182—183°/0·65 mm. (Found: C, 85·0; H, 8·5. $C_{18}H_{22}O$ requires C, 85·1; H, 8·7%), were the intermediates.

4-*neo*Pentyldiphenylmethyl chloride,[3] b. p. 179°/1·0 mm. (Found: Cl, 12·9. Calc. for $C_{18}H_{21}Cl$: Cl, 13·0%), was prepared from **4-*neo*pentylbenzophenone,** b. p. 213—215°/20 mm., needles, m. p. 84° (from light petroleum) (Found: C, 85·2; H, 7·8. Calc. for $C_{18}H_{20}O$: C, 85·7; H, 7·9%). The intermediate, **4-*neo*pentyldiphenylmethyl alcohol,** b. p. 168—170°/0·5 mm., separated from light petroleum in needles, m. p. 82—83° (Found: C, 84·7; H, 8·9. Calc. for $C_{18}H_{22}O$: C, 85·0; H, 8·7%); addition of the ketone depressed the m. p.

[4] Baddeley, *J.*, 1944, 236.
[5] Grunert, Nichol, and Sandin, *J. Amer. Chem. Soc.*, 1947, **69**, 2255.
[6] Hughes, Ingold, and Taher, *J.*, 1940, 949.
[7] Baddeley and Varma, *J.*, 1957, 2727.
[8] Bielefeldt, *Annalen*, 1879, **198**, 385.

XUM

Diphenylmethyl chloride and its 4-methyl, 4-ethyl, 4-propyl (Found: Cl, 14·3. Calc. for $C_{18}H_{21}Cl$: Cl, 14·5%), and 4-*iso*butyl (Found: Cl, 13·5. Calc. for $C_{17}H_{19}Cl$: Cl, 13·7%) derivatives were similarly obtained.[3,6]

Kinetic Measurements.—The method employed was that described by Hughes, Ingold, and Taher [6] for alcoholysis in anhydrous ethyl alcohol. Approximately 0·01M-solutions were used. The first-order rate constants (sec.$^{-1}$) are summarised in the Tables. Each rate constant represents the average of several values.

MANCHESTER COLLEGE OF SCIENCE AND TECHNOLOGY,
MANCHESTER, 1.

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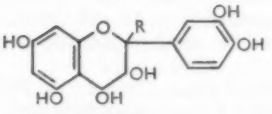
644. *The Constitution of the* leuco*Anthocyanidin, Peltogynol.*

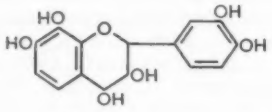
By W. R. CHAN, W. G. C. FORSYTH, and C. H. HASSALL.

New evidence leads to the proposal that the structure of the *leuco*anthocyanidin peltogynol should be modified to (IV), which relates it to the flavan-3 : 4-diols. The stereochemistry of peltogynol and an isomer, peltogynol B, which accompanies it in the extract of *Peltogyne porphyrocardia*, is discussed.

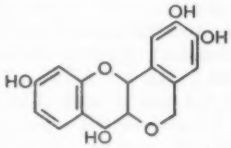
THERE is extensive evidence of the occurrence in plant tissue of colourless substances that afford anthocyanidin-like pigments on treatment with acids.[1] There is relatively little direct evidence, however, concerning the molecular structures of these *leuco*anthocyans and *leuco*anthocyanidins. Robinson and Robinson [1] suggested that *leuco*cyanidin might be formulated as (I). Elucidation [2] of the structure of melacacidin as (II) and the observation that cyanidin chloride is readily formed from the corresponding flavan-3 : 4-diol (III) on treatment with acid [3] in the presence of oxygen, have led to the proposal [2,3] that natural *leuco*anthocyanidins are derivatives of flavan-3 : 4-diols. However, the constitution assigned earlier [4] to peltogynol, a constituent of the heartwood of *Peltogyne porphyrocardia* and the first *leuco*anthocyanidin to be isolated, is at variance with this hypothesis. We have studied some further reactions of peltogynol and suggest the structure (IV) which may be regarded as being derived from a flavan-3 : 4-diol.



(I) : R = OH
(III) : R = H



(II)



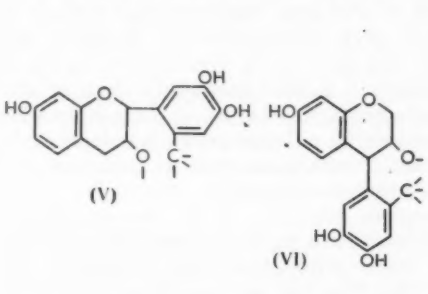
(IV)

Robinson and Robinson's structure [4] (VII) for peltogynol, $C_{16}H_{14}O_6$, was based largely on the following evidence. The substance is optically active. It forms a pyrylium salt. It gives tetra-acyl derivatives but a trimethyl ether which is insoluble in alkali and gives no colour with ferric chloride solution, which suggests that one of the four hydroxyl groups is non-phenolic. As peltogynol gives a 2 : 4-dinitrophenylhydrazone it appears that this hydroxyl group is associated with a semi-acetal structure. Nitric acid oxidises peltogynol to 2 : 4 : 6-trinitroresorcinol, and tri-*O*-methylpeltogynol to 4 : 5-dinitroveratrole, while treatment of tri-*O*-methylpeltogynol with potassium permanganate yields *m*-hemipinic acid, showing that peltogynol contains a resorcinol as well as a catechol nucleus which has

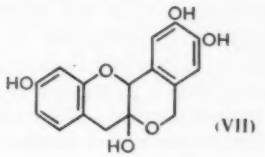
[1] Robinson and Robinson, *Biochem. J.*, 1933, **27**, 206.
[2] King and Bottomley, *J.*, 1954, 1399.
[3] Bauer, Birch, and Hillis, *Chem. and Ind.*, 1954, 433.
[4] Robinson and Robinson, *J.*, 1935, 744.

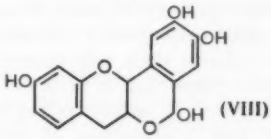
carbon atoms attached to positions 4 and 5. The similarity of peltogynidin chloride to known anthocyanidins suggested that the skeletons (V) and (VI) should be considered. *X*-Ray data favoured (V) as it was difficult to arrange models based on (VI). The free hydroxyl group of the resorcinol nucleus was placed at position 7 and not 5 in view of the fluorescent properties of the methylated peltogynidin salts. Alternative structures (VII) and (VIII) were suggested but the former was favoured on the grounds that a compound with the structure (VIII) resembles catechin and should, therefore, be relatively resistant to the formation of a flavylium salt.

Although these reactions make it evident that peltogynol contains both a catechol and a resorcinol nucleus in a C_6–C_3–C_6 flavonoid structure they do not define the substitution on the C_3 portion with certainty. It appeared possible that the formation of the 2 : 4-dinitrophenylhydrazone from peltogynol could be attributed to oxidation of an alcohol group in an activated position. We have obtained support for this view from experiments on the oxidation of trimethylpeltogynol with manganese dioxide in chloroform. The product, tri-*O*-methylpeltogynone, $C_{19}H_{18}O_6$, is optically active and gives a cherry-red colour with magnesium–hydrochloric acid. Treatment with sodium borohydride regenerates the original tri-*O*-methylpeltogynol. The infrared absorption spectrum of trimethylpeltogynone shows no maximum in the hydroxyl stretching region but a band


(V)

(VI)


(VII)


(VIII)

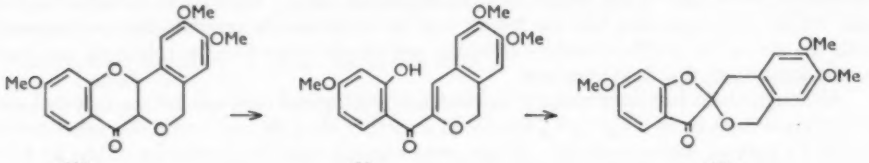
at 1687 cm.$^{-1}$ is in the position expected of a carbonyl group conjugated to an aromatic nucleus and lying in a six-membered ring.[5] The ultraviolet absorption spectrum is typical of compounds in which a carbonyl group is in conjugation with a resorcinol or a phloroglucinol nucleus.[6] This evidence led us to favour the structure (IX) for tri-*O*-methylpeltogynone. In support of this tri-*O*-methylpeltogynol was converted by alkali almost quantitatively into a yellow, alkali-soluble compound $C_{19}H_{18}O_6$ with the properties of the chalcone (X). It gives an alkali-insoluble methylation product $C_{20}H_{20}O_6$ and a colourless dihydro-derivative with ketonic properties. The carbonyl bands in the infrared spectrum of the chalcone and the methylation product are at 1615 and 1650 cm.$^{-1}$ respectively. The shift in wavelength is that expected when comparing a hydrogen-bonded 2′-hydroxychalcone with the corresponding 2′-methoxychalcone.[7] The chalcone was converted by dilute sulphuric acid into an isomer which is assigned structure (XI) on the basis of a negative magnesium–hydrochloric acid test, resistance to acetylation, and an infrared absorption spectrum with no hydroxyl bands but with a carbonyl band[8] at 1720 cm.$^{-1}$.

Oxidation of the chalcone (X) with potassium permanganate yielded 2-hydroxy-4-methoxybenzoic acid. This confirms Robinson and Robinson's placing of the hydroxyl group at position 7.

[5] Shaw and Simpson, *J.*, 1955, 655.
[6] Morton and Sawires, *ibid.*, 1940, 1052; Valyashko and Rozum, *J. Gen. Chem.* (*U.S.S.R.*), 1947, **17**, 783.
[7] Hergert and Kurth, *J. Amer. Chem. Soc.*, 1953, **75**, 1622.
[8] Gutsche, *ibid.*, 1951, **73**, 786.

XUM

The new information leads unambiguously to structure (IV) for peltogynol. It could arise biogenetically by condensation of formaldehyde (or its equivalent) with the corresponding flavan-3 : 4-diol.[9] There are various biogenetic schemes in which similar condensations with formaldehyde are postulated.[10] Among flavonoids, peltogynol shares



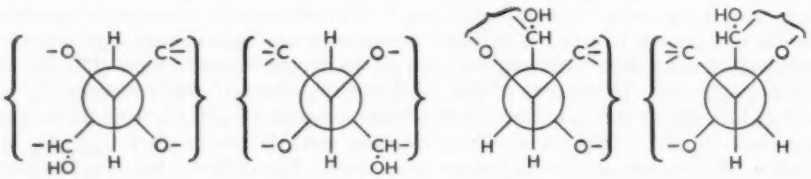
(IX) (X) (XI)

with distemonanthin [11] the unusual attachment of a carbon substituent to the 2′-position of the aromatic ring attached to the benzopyran nucleus.

Attention has already been drawn to the necessity of including an oxidation in the conversion of peltogynol into peltogynidin. There is experimental evidence for this. Hydrolysis of peltogynol with dilute acid, in an inert atmosphere, gives less than 1% of peltogynidin but, in the presence of oxygen, a yield of more than 80% has been obtained.

Aqueous extracts of the heartwood of *Peltogyne porphyrocardia* contain a second *leuco*anthocyanidin, peltogynol B, which yields peltogynidin on treatment with acid. Its relation to peltogynol is clear from oxidation of its trimethyl derivative to tri-*O*-methylpeltogynone: peltogynol and peltogynol B differ only in the mode of attachment of the 4-hydroxyl group. As tri-*O*-methylpeltogynol is formed exclusively when tri-*O*-methylpeltogynone, with a relatively unhindered carbonyl group, is reduced with sodium borohydride, peltogynol must be assigned a constitution with an equatorial 4-hydroxyl group [12] while peltogynol B has an axial 4-hydroxyl group.

The evidence does not permit complete definition of the stereochemistry of the peltogynols. However, it favours limitation to two pairs of isomers (XIIa, b) and (XIIc, d). Peltogynol B, unlike peltogynol, yields peltogynidin when heated in air at the relatively low temperature of 130°. This reaction involves elimination of the axial 4-hydroxyl group. It will occur most readily when the 3-hydrogen atom, the 4-hydroxyl



(XIIa) (XIIb) (XIIc) (XIId)

group, and the 3- and 4-carbon atoms are coplanar.[12] This is achieved when both the 3-hydrogen atom and 4-hydroxyl group have axial conformations. The relation between peltogynol and peltogynol B indicates that peltogynol has also an axial 3-hydrogen atom.

Peltogynol has one of the structures (XIIa—d) in which the 4-hydroxyl group is equatorial; peltogynol B has the corresponding structure with an axial hydroxyl group.

Experimental

M. p.s were determined by means of a Kofler block and are uncorrected. Rotation measurements employed chloroform solutions at 28—30° except where other solvents are specified.

[9] Keppler, *J.*, 1957, 2721; Roux, *Chem. and Ind.*, 1958, 161; White and King, *ibid.*, p. 291.
[10] Robinson, "The Structural Relations of Natural Products," Oxford Univ. Press, 1955; Woodward, *Angew. Chem.*, 1956, **68**, 13.
[11] King, King, and Stokes, *J.*, 1954, 4594.
[12] Barton, *J.*, 1953, 1027.

Ultraviolet spectra were determined for EtOH solutions on a Beckman spectrophotometer, model D.U. Infrared spectra were measured with potassium bromide discs unless otherwise stated. We are grateful to Dr. S. M. Nagy, Massachusetts Institute of Technology, and Dr. H. E. Hallam, University College, Swansea, for the determinations of infrared absorption spectra.

Isolation of Peltogynol and Peltogynol B by Partition Chromatography.—Fresh sawdust (500 g.) of *Peltogyne porphyrocardia* heartwood was stirred with successive amounts of water (8 l., 5 l., 5 l.) on a steam-bath for 20 min. each. The extraction, filtration, and all subsequent operations were carried out in apparatus shielded from light. Paper chromatography on Whatman No. 1 paper with (*A*) butan-1-ol–acetic acid–water (4 : 1 : 5) [13] or with water [14] showed the presence of the two major phenolic components: peltogynol [R_F (H_2O) 0·04; (*A*) 0·45] and peltogynol B [R_F (H_2O) 0·10; (*A*) 0·52]. The phenols were detected with a ferric chloride–potassium ferricyanide spray.[15] Peltogynol and peltogynol B were present in the crude aqueous extract in the ratio 4 : 3 when determined by quantitative paper chromatography with permanganate titration.[16]

The combined extract was added to a column (25 × 10 cm.) of dry cellulose powder (Solka floc.; 200 mesh) which was developed with water. The first 9 l. of eluate contained no peltogynol B and was discarded. The following 5760 c.c. contained only peltogynol B. The following 9240 c.c. contained both peltogynol and peltogynol B, and the final 5020 c.c. contained only peltogynol. Each of the two fractions containing peltogynol B was saturated with sodium chloride and extracted twice with one-quarter of its volume of ethyl acetate. The extracts were dried (Na_2SO_4–$NaHCO_3$, 1 : 1), concentrated under reduced pressure to approximately 150 c.c., and poured into light petroleum (1 l.; b. p. 40—60°). Peltogynol B (2·85 g.), the precipitate from the first fraction, recrystallized from chloroform, containing 2·5% (v/v) of ethanol, as colourless prisms which held chloroform tenaciously even at 100°.

The mixed fraction was worked up for peltogynol by Robinson and Robinson's method.[4] The last aqueous fraction, containing only peltogynol, was directly concentrated *in vacuo* without decomposition. It crystallized from the aqueous concentrate (yield 4·63 g.) and had $[\alpha]_D^{21}$ +273° (*c* 0·6 in ethyl acetate) (Found: C, 63·6; H, 4·7. Calc. for $C_{16}H_{14}O_6$: C, 63·6; H, 4·6%).

Peltogynidin.—Treatment of peltogynol with acid gave two coloured products, peltogynidin and so-called phlobaphen. The yield of peltogynidin was determined in the following way. The solution obtained when peltogynol (10 mg.) was heated with dilute hydrochloric acid was added to a cellulose powder column (10 × 2 cm.) and washed with N-hydrochloric acid (5 × 2 c.c.). The colour was all adsorbed on the top 2 cm. of the column. Butanol (12 c.c.) equilibrated with an equal volume of N-hydrochloric acid was then added. The peltogynidin band separated from the faster-moving phlobaphen band. The column was extruded. The peltogynidin band was cut out and extracted with methanolic 0·1N-hydrochloric acid. The colour intensity of the solution was compared with a standard prepared from crystalline peltogynidin chloride.

The maximum yield (11·5 ± 0·5%) by this procedure was obtained by using 2N-hydrochloric acid for 15 min. at 100°. The production of phlobaphen, but not peltogynidin, was greatly increased by increasing the concentration of acid or the time of heating, or substituting alcoholic for aqueous acid.

However, when oxygen was bubbled through the heated mixture, yields of peltogynidin of over 80% were obtained. When nitrogen was used the yield was less than 1%. Peltogynol and peltogynol B gave very similar yields of peltogynidin.

Peltogynidin gives R_F values on paper which differ from the common anthocyanidins which occur in flower pigments: Butan-1-ol–acetic acid–water (4 : 1 : 5), 0·65; butanol–2N-HCl, 0·38; "Forestal" solvent, 0·72. Unlike the common anthocyanidins it was stable during chromatography in butanol–acetic acid–water. When 100 mg. of peltogynol were boiled with acid as above and chromatographed on a column, crystalline peltogynidin hydrochloride (64 mg.) was recovered (Found: C, 54·3; H, 4·5; Cl, 9·7. Calc. for $C_{16}H_{11}O_5Cl,2H_2O$: C, 54·0; H, 4·2; Cl, 10·0%).

[13] Partridge, *Biochem. J.*, 1948, **42**, 238.
[14] Roberts and Wood, *ibid.*, 1953, **53**, 332.
[15] Barton, Evans, and Gardner, *Nature*, 1952, **170**, 249.
[16] Forsyth, *Biochem. J.*, 1955, **60**, 108.

XUM

Tri-O-methylpeltogynol.—This was prepared most conveniently from a crude extract of *Peltogyne porphyrocardia*. It was identical with material prepared from pure peltogynol by Robinson and Robinson's procedure.[4]

The ethyl acetate-soluble fraction was methylated with diazomethane, and purified by chromatography in benzene–chloroform (9 : 1) on ethyl acetate-washed alumina.[7] *Tri-O-methylpeltogynol* has m. p. 203—205°, $[\alpha]_D$ +250° (*c* 1·4), $\lambda_{max.}$ 280 and 286 mμ (log ε 3·84 and 3·87 respectively), $\nu_{max.}$ 3484 cm.$^{-1}$ [Found: C, 66·35; H, 5·9; O, 27·7; OMe, 27·6%; *M*, 332. $C_{16}H_{11}O_3(OMe)_3$ requires C, 66·3; H, 5·85; O, 27·9; OMe, 27·0%; *M*, 344]. The compound gave no colour with ferric chloride but a violet colour with the Fearon–Mitchell reagent. An alcoholic solution quickly gave a red solution with a green fluorescence on addition of a few drops of hydrochloric acid.

The *acetate* was prepared in the usual way with fused sodium acetate and acetic anhydride. It crystallized from light petroleum (b. p. 60—80°)–benzene or from aqueous acetic acid, as white needles, m. p. 154—156° [Found: C, 65·7; H, 5·8; OMe, 24·15. $C_{16}H_{13}O_4(OMe)_3$ requires C, 65·3; H, 5·7; OMe, 24·1%].

Tri-O-methylpeltogynone.—Manganese dioxide[18] (14 g.) was added to a solution of tri-*O*-methylpeltogynol (1·0 g.) in chloroform (125 c.c.). The suspension was stirred at room temperature for 18 hr., then filtered. The manganese dioxide was washed with chloroform (100 c.c.), and the combined filtrates were evaporated to dryness. The white residue, after one recrystallization from ethanol, afforded needles (685 mg.), m. p. 211—213°, $[\alpha]_D$ +279° (*c* 1·2) [Found: C, 66·5; H, 5·4; O, 28·0; OMe, 27·0. $C_{16}H_9O_3(OMe)_3$ requires C, 66·6; H, 5·3; O, 27·9; OMe, 27·2%], $\lambda_{max.}$ 276 mμ (log ε 4·23), infl. 230 and 306 mμ (log ε 4·30 and 3·87 respectively), $\nu_{max.}$ 1687 cm.$^{-1}$ (CO) (in $CHCl_3$). The compound was recovered unchanged after attempted acetylation by acetic anhydride–sodium acetate. It gave no colour with ferric chloride or with the Fearon–Mitchell reagent. Attempted oximation in a solution buffered with sodium acetate gave unchanged material. The ketone dissolves in hot hydrochloric acid to a yellow solution. Reduction of an ethanolic solution with magnesium and hydrochloric acid gave an immediate cherry-red colour.

Reduction of Tri-O-methylpeltogynone with Sodium Borohydride.—A solution of sodium borohydride (25 mg.) in water (2 c.c.) was added to a suspension of the ketone (20 mg.) in methanol. The suspension started clearing immediately. The solution was shaken for 2 hr., then diluted with water (10 c.c.). After filtration and washing with water, the residue was dried and recrystallized from benzene as white needles, m. p. 202—203° alone or mixed with natural tri-*O*-methylpeltogynol.

Degradation of Tri-O-methylpeltogynone with Alkali.—A stirred suspension of the ketone (300 mg.) in 10% aqueous potassium hydroxide (72 c.c.) was heated on a boiling-water bath for 75 min. The orange solution was filtered and acidified, to give a yellow precipitate which was collected after 12 hr. This (298 mg.) had m. p. 121—124° and recrystallized from ethanol to give the chalcone, 3-(2-*hydroxy*-4-*methoxybenzoyl*)-6 : 7-*dimethoxy*isochromen (X) as golden-yellow plates, m. p. 124—125°, $\lambda_{max.}$ 251, 295, and 395 mμ (log ε 4·07, 4·05, and 4·31 respectively), $\nu_{max.}$ 1615 cm.$^{-1}$ (CO) [Found: C, 66·6; H, 5·3; O, 27·7; OMe, 27·55. $C_{16}H_9O_3(OMe)_3$ requires C, 66·7; H, 5·3; O, 28·0; OMe, 27·2%]. It gave a brown colour with ferric chloride. There was no change in colour in the magnesium–hydrochloric acid test.

Oxidation of 3-(2-*Hydroxy*-4-*methoxybenzoyl*)-6 : 7-*dimethoxy*isochromen *with Potassium Permanganate.*—5% Aqueous potassium permanganate (30 c.c.) was added, with vigorous stirring, at room temperature to a solution of the chalcone (X) (425 mg.) in acetone (50 c.c.). Stirring was continued for a further 6 hr., then the mixture was left undisturbed for 12 hr. The supernatant solution was then completely colourless. After dissolution of the suspended solid by sulphur dioxide, the solution was treated with dilute sulphuric acids, warmed on a water-bath for 10 min., and cooled. The acetone was removed *in vacuo*. The product, which separated on cooling, recrystallized from benzene as white needles, m. p. 163—164° alone or mixed with 2-hydroxy-4-methoxybenzoic acid (Found: C, 57·2; H, 4·8; O, 38·1. Calc. for $C_8H_8O_4$: C, 57·1; H, 4·8; O, 38·1%). The infrared spectra of the "natural" and authentic 2-hydroxy-4-methoxybenzoic acid were identical over the region 2—15 μ.

3-(2 : 4-*Dimethoxybenzoyl*)-6 : 7-*dimethoxy*isochromen.—The chalcone (X) (100 mg.) was methylated with dimethyl sulphate and 10% aqueous potassium hydroxide. The product

[17] Mancera, Barton, Rozenkranz, and Djerassi, *J.*, 1952, 1021.
[18] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *ibid.*, p. 1097.

crystallized from benzene–light petroleum (b. p. 60—80°) as pale yellow hexagonal plates (55 mg.), m. p. 137—138°, $\lambda_{max.}$ 252 and 375 mμ (log ε 4·19 and 4·24 respectively), infl. 315 mμ (log ε 3·85), $\nu_{max.}$ 1650 cm.$^{-1}$ (CO) [Found: C, 67·6; H, 5·8; O, 27·1; OMe, 35·3. $C_{16}H_8O_3(OMe)_4$ requires C, 67·4; H, 5·7; O, 26·9; OMe, 34·8%]. In ethanol it gave no colour with ferric chloride.

3-(2-*Hydroxy*-4-*methoxybenzoyl*)-6 : 7-*dimethoxy*isochroman.—The ketone (X) (81 mg.) was hydrogenated in ethyl acetate with 10% palladium–charcoal (104 mg.). One mol. of hydrogen was taken up smoothly. The residue, after removal of catalyst and solvent, crystallized from ethanol as colourless needles, m. p. 139—140°, $\lambda_{max.}$ 230 mμ (log ε 4·24) (Found: C, 66·45; H, 5·85; O, 27·6. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·85; O, 27·9%). It gave a brown colour with ferric chloride.

Action of Sulphuric Acid on 3-(2-*Hydroxy*-4-*methoxybenzoyl*)-6 : 7-*dimethoxy*isochromen.—A solution of the compound (X) (200 mg.), ethanol (20 c.c.), and 8N-sulphuric acid (10 c.c.) was heated on a boiling-water bath for 24 hr. Removal of ethanol *in vacuo* gave 2 : 3-*dihydro*-6 : 6′ : 7′-*trimethoxy*-3-*oxobenzofuran*-2-spiro-3′-iso*chroman* (XI) which recrystallized as white needles, m. p. 183—185° (from ethanol), $\lambda_{max.}$ 232, 278, and 322 mμ (log ε 4·26, 4·23, and 3·98, respectively) [Found: C, 66·6; H, 5·6; O, 28·3; OMe, 27·7. $C_{19}H_8O_3(OMe)_3$ requires C, 66·7; H, 5·3; O, 28·0; OMe, 27·2%]. The compound gave no ferric chloride colour and was insoluble in aqueous sodium hydrogen carbonate or warm 10% potassium hydroxide solution. Attempted acetylation (pyridine–acetic anhydride) gave unchanged material. It gave no colour in the magnesium–hydrochloric acid test.

Periodic Acid Oxidation of Tri-O-*methylpeltogynol and Tri*-O-*methylpeltogynone.*—0·773M-Periodic acid (1 c.c.) was added to a solution of the derivative (25 mg.) in ethanol (20 c.c.) and was estimated in the usual way. There was no uptake of periodic acid.

Peltogynol B (*with* J. B. Roberts).—Our product had $[\alpha]_D$ +270°, m. p. 130—140° (decomp. with formation of about 15% of peltogynidin). Satisfactory analyses have not been obtained on the crystalline material from chloroform owing to retention of solvent. The *tetra-acetate*, prepared with pyridine and acetic anhydride, crystallized from ethanol as white needles, m. p. 240°, $[\alpha]_D$ +262° (Found: C, 61·2; H, 4·6; Ac, 35·0. $C_{16}H_{10}O_8Ac_4$ requires C, 61·3; H, 4·7; Ac, 36·6%).

Tri-O-*methylpeltogynol B* was obtained by methylation of peltogynol B with diazomethane as needles, m. p. 140° [Found: C, 66·6; H, 5·9; OMe, 26·6. $C_{16}H_{11}O_3(OMe)_3$ requires C, 66·3; H, 5·8; OMe, 27·0%], $\lambda_{max.}$ 283 mμ (log ε 3·82). Its *monoacetate*, prepared with pyridine and acetic anhydride, and crystallized from ethanol, had m. p. 182° [Found: Ac, 13·0. $C_{16}H_{10}O_3Ac(OMe)_3$ requires Ac, 12·9%].

Peltogynol B (0·77 g.) was heated at 70° for 1 hr. in 1% aqueous oxalic acid. The solution so obtained was fractionated on a cellulose column for isolation of peltogynol and peltogynol B as described above. Peltogynol (0·25 g.) and unchanged peltogynol B (0·24 g.) were isolated. When peltogynol (2 g.) was heated at 70° for 1 hr. in 1% aqueous oxalic acid, peltogynol B (0·25 g.) and unchanged peltogynol (1·2 g.) were isolated. The products were identified by conversion into the tetra-acetates and by mixed m. p. determination.

Tri-*O*-methylpeltogynol B (0·33 g.) was oxidised with manganese dioxide in chloroform according to the procedure for trimethylpeltogynol. The product, after crystallization from ethanol, yielded needles (0·1 g.), m. p. and mixed m. p. 211°, $[\alpha]_D$ +280°. Reduction with sodium borohydride then gave tri-*O*-methylpeltogynol, m. p. and mixed m. p. 203°. The chalcone, prepared by treatment with alkali, was identical with that from tri-*O*-methylpeltogynone.

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Department of Chemistry, University College of Swansea.
Colonial Microbiological Research Institute, Trinidad.
University College of the West Indies, Jamaica. [*Received, April 15th,* 1958.]

XUM

645. *Intermediates in the Conversion of Pinonic Acid into Carbocyclic Compounds.*

By C. L. Arcus and G. J. Bennett.

The cyclisation of pinonic acid in acidic media, leading to compounds containing benzene, *cyclo*hexane, and *cyclo*hexene rings, has been investigated. The reactions with bromine and hydrochloric acid, and with phosphoric acid, are believed to follow the courses shown respectively by the left- and the right-hand sides of the scheme (I—XIII).

Barbier and Grignard [1] found 2 : 4-dimethylphenylacetic acid (VII) to be formed by the action of bromine on pinonic acid (I). It is apparent that several consecutive reactions are probably involved in so considerable a change in structure. Harispe [2] increased the yield by allowing bromine and pinonic acid to react in concentrated hydrochloric acid to form a homogeneous solution, then heating it, and subsequently isolating the product (VII) as its methyl ester. By adding the solution, above, to ice, he obtained an oil which, though otherwise unidentified, contained bromine in quantity approximating to that required for a monobromopinonic acid or a monobromo-derivative of 3-(1-hydroxy-1-methylethyl)-6-oxoheptanoic lactone (III). He also converted the ketone (III) into 2 : 4-dimethylphenylacetic acid, an intermediate bromine-containing oil similar to the last again being isolable.

Harispe proposed the following reaction scheme: Pinonic acid is converted into bromopinonic acid (II) which rearranges to the bromo-ketone (IV); this compound, by loss of water and hydrogen bromide, forms the lactone (VIII), hydrolysis of which to the corresponding hydroxy-acid and dehydration of the latter yield 2 : 4-dimethylphenylacetic acid. For the reaction commencing with the ketone (III), bromination to (IV) is the first stage.

The mechanism of the rearrangement of pinonic acid to the ketone (III) having been investigated,[3] it was decided to attempt to elucidate the mechanism of the reaction above by the isolation of intermediates and by separation of the oxidation and acid-catalysis.

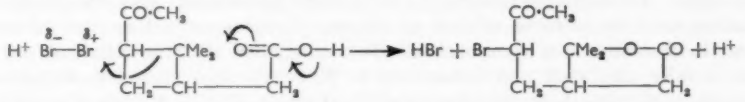
Repetition, with (±)-*trans*-pinonic acid, of Harispe's procedure gave 2 : 4-dimethylphenylacetic acid in 50% yield; also, separation by esterification was replaced by direct extraction with dilute ammonia, followed by sublimation, the acid being then obtained in 66% yield. The latter isolation shows 2 : 4-dimethylphenylacetic acid to be the end-product of the reaction and eliminates the possibility that the isomeric lactone (VIII) is the actual product, which on treatment with methanolic hydrogen chloride would be converted into methyl 2 : 4-dimethylphenylacetate. 2 : 4-Dimethylphenylacetic acid (57%) has also been obtained by direct extraction from the reaction commencing with ketone (III).

From the product of bromination of pinonic acid at $<30°$ there was isolated a crystalline bromopinonic acid. On being heated with hydrochloric–hydrobromic acid approximating in composition to the solvent present after bromine-substitution has taken place, it gave 2 : 4-dimethylphenylacetic acid in 56% yield. Reduction of the bromo-acid with zinc and hydrochloric acid gave (±)-*trans*-pinonic acid and the ketone (III), isolated as the oxime and the 2 : 4-dinitrophenylhydrazone respectively; production of the former demonstrates that the bromo-acid has the pinonic acid structure and the *trans*-configuration; the formation of the ketone (III) is ascribed to rearrangement of pinonic acid in the acidic reduction medium. No compound containing a bromomethyl group has been encountered and, further, acid-catalysed bromination of menthone and carvomenthone yields exclusively

[1] Barbier and Grignard, *Compt. rend.*, 1909, **148**, 646.
[2] Harispe, *Ann. Chim.*, 1936, **6**, 249.
[3] Arcus and Bennett, *J.*, 1955, 2627.

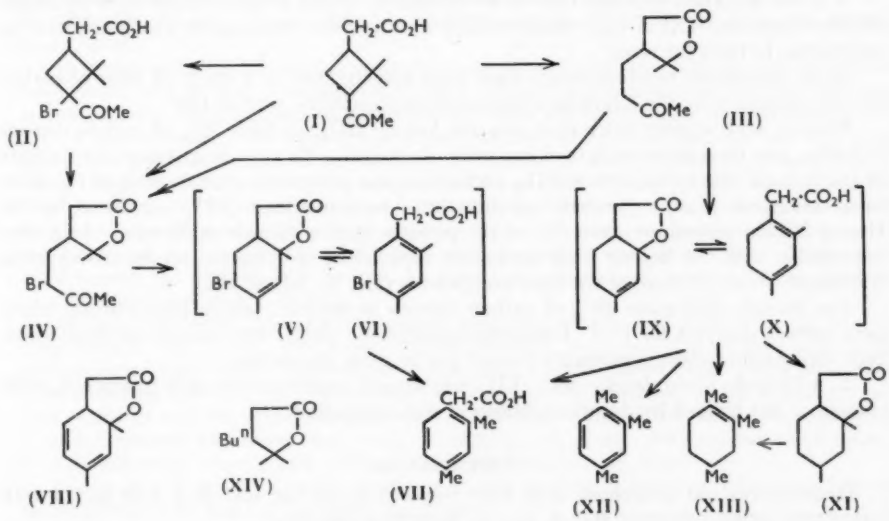
the tertiary bromo-derivatives;[4] the bromopinonic acid is therefore assigned the structure (II).

Further, it has been found that conversion of pinonic acid into the ketone (III) is too slow for this to be the main course of reaction (the ketone, once formed, is rapidly brominated). It is concluded that the bromo-ketone is largely formed either by rearrangement of bromopinonic acid (which rapidly disappears if the temperature is not kept below 30°) or directly by the reaction of bromine with pinonic acid under acidic conditions:



this mechanism is analogous to that deduced[3] for the acid-catalysed rearrangement of pinonic acid to the ketone (III).

From Harispe's and the present results, the scheme (I—VII) is deduced. The bromo-ketone (IV), regarded as the essential precursor to 2 : 4-dimethylphenylacetic acid, is formed from pinonic acid by three routes: through bromopinonic acid (II), through the ketone (III), and directly, as above. Ring-closure yields the lactone (V), in equilibrium with the acid (VI), and from these 2 : 4-dimethylphenylacetic acid is formed by elimination of hydrogen bromide.



The ketone (III) is rapidly formed when pinonic acid is heated in phosphoric acid at 100° (92—95% in 5 min.[3]), and cyclisation occurs on further heating at higher temperatures, analogously to the change (IV) ⟶ (V) + (VI).

(±)-*trans*-Pinonic acid was heated in phosphoric acid to 165°, evolution of carbon dioxide commencing at 150°; 2 : 4-dimethylphenylacetic acid was obtained in 3·5% yield; there was isolated also a lactone which, from the analytical data, equivalent on hydrolysis, and oxidation by bromine to 2 : 4-dimethylphenylacetic acid, is considered to have structure (XI) (yield 7·5%); there were also a hydrocarbon mixture (yield 25%, calc. as C_9H_{16}), a higher-boiling hydrocarbon fraction (not identified), and considerable neutral resin. The first mixture is considered, on the following grounds,

[4] Kotz and Steinhorst, *Annalen*, 1911, **379**, 13.

to be composed of ψ-cumene (XII) and 1 : 2 : 4-trimethyl*cyclo*hexene (XIII) in approximately equal amounts: (*a*) Nitration gave 3 : 5 : 6-trinitro-ψ-cumene in 23% yield; ψ-cumene itself gave 60%. (*b*) A series of fractions showed the following properties: the highest-boiling gave 49% of the same trinitro-compound, those of lower b. p.s 5%; but a fraction boiling below these last gave, after aromatisation with palladised charcoal, 28%. Analytical data for a lower-boiling fraction are consistent with the presence of much trimethyl*cyclo*hexene together with some ψ-cumene. (*c*) Rates of hydrogenation of *cyclo*hexene, 1-methyl*cyclo*hexene, 1 : 2-dimethyl*cyclo*hexene, and the (unfractioned) hydrocarbon were found to be related as follows: *cyclo*hexene $\gg$ 1-methyl*cyclo*hexene $\gg$ 1 : 2-dimethyl*cyclo*hexene $\approx$ hydrocarbon. It is concluded that the ethylenic part of the molecule is fully alkylated, and hence that 1 : 2 : 4-trimethyl*cyclo*hexene is present, but not its isomers or trimethyl*cyclo*hexadienes, all of which contain the more readily hydrogenated CH:CH or CH:CMe groups.

The reaction scheme (I—XIII), accounting for the formation of the products described, is put forward. Pinonic acid is converted into the ketone (III), which cyclises to the lactone (IX), an equilibrium existing between this compound and the acid (X). The lactone (XI) is formed by addition of hydrogen to (IX), while dehydrogenation of (X) [or (IX) directly] yields 2 : 4-dimethylphenylacetic acid (VII). Decarboxylation of (IX) [or (X)] together with addition of hydrogen yields 1 : 2 : 4-trimethyl*cyclo*hexene (XIII); accompanied by dehydrogenation it yields ψ-cumene (XII).

It is not intended to imply that there necessarily occurs a dismutation of, or hydrogen transfer between, (IX) or (X); such transfer may involve compounds which condense or polymerise to form the resin.

Some alternative reaction routes have been investigated by a study of rates of carbon dioxide evolution by the following compounds in phosphoric acid at 160°.

Pinonic acid, rapidly converted into the ketone (III), yielded 54% of carbon dioxide in 5 min., but thereafter the rate of evolution slackened. To gain insight into the stability of the lactone ring in the ketone (III), cyclisation was prevented by reduction of the keto- to a methylene group; β-*n*-butyl-γγ-dimethyl-γ-butyrolactone (XIV), obtained by the Huang-Minlon procedure, gave 5% of the possible carbon dioxide in 30 min. It is thus improbable that the ketone itself undergoes rapid decarboxylation; so decarboxylation is referred to one or more of the later compounds (IX, X, XI, or VII).

The lactone (XI) gave 39% of carbon dioxide in 60 min., and a hydrocarbon which gave correct analyses for 1 : 2 : 4-trimethyl*cyclo*hexene (XIII) was isolated in small yield; thus, this hydrocarbon is probably formed partly from this lactone.

2 : 4-Dimethylphenylacetic acid (VII) was almost unaffected by such treatment, so ψ-cumene is not formed by decarboxylation of this compound.

Experimental

Hydrochloric and phosphoric acid refer respectively to the acid of *d* 1·18 and *d* 1·74. Extraction, unless otherwise stated, was by methylene chloride.

Bromine–Hydrochloric Acid Reactions.—(*a*) In each of the following experiments (±)-*trans*-pinonic acid [3] (18·4 g.) was suspended in hydrochloric acid (30 ml.), and bromine (16·5 g.) was added in one portion; the flask was shaken vigorously, the temperature reaching 48° in 10 min., with disappearance of the pinonic acid and bromine. The solution was heated in a steam-bath for 4 hr., then cooled. Either of two procedures was then used.

(i) Water (70 ml.) was added, and the resin which separated was dissolved in methylene chloride (30 ml.); the aqueous solution was repeatedly extracted (total solvent, 80 ml.). The combined methylene chloride solutions were washed with water, excess of dilute aqueous ammonia, then again water, and on evaporation gave an unidentified oil (1·3 g.); the ammoniacal solution and the succeeding washings were acidified with hydrochloric acid and extracted (3 × 30 ml.). The extract was washed with water and the solvent distilled; the product (15·3 g.) was sublimed at 100°/0·01 mm. during 5 hr., and yielded 2 : 4-dimethylphenylacetic acid (10·8 g.), m. p. 101°; after recrystallisation from *cyclo*hexane it (10·2 g.) had m. p. 104°.

The residue from sublimation was boiled with chloroform, then cooled and an insoluble powder was filtered off; this material was twice crystallised from aqueous ethanol, and its solution in acetone decolorised by passage through a column of charcoal, followed by washing of the column with this solvent. The product (0·47 g.) yielded, after three recrystallisations from acetone, an acid (*A*), m. p. 214° [Found: C, 72·95; H, 6·9%; *M* (Rast), 309].

(ii) The solid which separated when the hydrochloric acid solution was cooled was collected on a sintered-glass filter, washed with hydrochloric acid, and added to methanol (15 ml.). The liquid was saturated with hydrogen chloride and boiled under reflux for ½ hr.; next day it was again saturated, and boiled for 1 hr. Water was added and the whole extracted; the extract was washed with water and dried (Na_2SO_4). It yielded methyl 2 : 4-dimethylphenylacetate (10·0 g.), b. p. 174—178°/95 mm.; a portion, left in contact with potassium carbonate, gave on distillation the ester, b. p. 124—126°/13 mm.; a further portion (5·0 g.) was boiled under reflux for 1 hr. with potassium hydroxide (2·0 g.), water (20 ml.), and ethanol (5 ml.). After cooling and acidification, recrystallisation of the product from hot water yielded 2 : 4-dimethylphenylacetic acid (4·1 g.), m. p. 105·5°. S-*Benzylthiuronium* 2 : 4-*dimethylphenylacetate*, plates (from water), had m. p. 164·5° (Found: S, 9·45. $C_{18}H_{22}O_2N_2S$ requires S, 9·7%).

(*b*) (±)-*trans*-Pinonic acid (19·0 g.) was added to bromine (16·5 g.) and hydrochloric acid (30 ml.) with cooling so that the temperature did not rise above 30°. After 10 min. the solution was poured on ice, and the aqueous liquid was decanted from a heavy oil, which was taken up in methylene chloride (50 ml.); this solution was washed with water, dried (Na_2SO_4), and evaporated; by filtration of the semi-solid residue, crystals (5·9 g.) were separated. After three recrystallisations from methylene chloride the product (2·85 g.) had m. p. 114·5—115°, and further recrystallisation yielded *bromopinonic acid*, m. p. 116·5—117° (Found: C, 45·9; H, 5·65; Br, 30·25%; equiv., 258. $C_{10}H_{15}O_3Br$ requires C, 45·65; H, 5·75; Br, 30·35%; equiv., 263).

To a vigorously stirred solution of the bromo-acid (0·25 g.) in hydrochloric acid (50 ml.) was added zinc dust (0·70 g.); subsequently water (50 ml.) and further zinc dust (0·70 g.) were added; stirring was continued for 5 hr., and the whole was kept overnight, then filtered. The filtrate was extracted; the extract was washed with dilute aqueous ammonia and with water, and gave a product (20 mg.) which was converted into its 2 : 4-dinitrophenylhydrazone (35 mg.) which, after recrystallisation from ethanol, had m. p. 162°, and m. p. 163° when mixed with the derivative, m. p. 163·5°, of the authentic ketone (III). The ammoniacal and aqueous washings were acidified and extracted; the product (50 mg.) from the extract was converted [3] into its oxime; the latter (10 mg.), m. p. 146—147°, had, after recrystallisation from ethyl acetate–carbon tetrachloride, m. p. 148—149°, and m. p. 149—150° when mixed with authentic (±)-*trans*-pinonic acid oxime of m. p. 152°.

Hydrogen chloride (17·5 g.) was passed into ice-cooled hydrochloric acid (69 ml.) and hydrobromic acid (*d* 1·48; free from bromine; 43 ml.); the product is referred to as hydrochloric–hydrobromic acid. Bromopinonic acid (0·50 g.) was heated under reflux on a steam-bath with this acid (2·0 ml.). From the clear solution first obtained, an oil separated; after 4 hr. water (3 ml.) was added and the whole was chilled. The oil solidified; the product was collected, washed with water, and dried. It (0·30 g.; m. p. 98—100°) yielded on sublimation 2 : 4-dimethylphenylacetic acid (0·25 g.), m. p. 103°, mixed m. p. 104°.

(*c*) Reaction as in (*b*), but without cooling, gave a syrup from which, in spite of seeding with bromopinonic acid, none of the latter was isolated.

(*d*) The (±)-ketone (III) (18·4 g.) was allowed to react with bromine and hydrochloric acid as in (*a*); reaction was rapid, the temperature rose to 50°, and a homogeneous solution was obtained; it was cooled. One half was treated as in (*a*, i) and yielded 2 : 4-dimethylphenylacetic acid (4·7 g.), m. p. 104° (105·5° after recrystallisation from *cyclo*hexane), and the acid *A* (0·25 g.), m. p. 203—205°. The rest was poured on ice and extracted. The extract, after being washed with water, dried (Na_2SO_4), and evaporated at reduced pressure, gave a syrup (12·7 g.), n_D^{25} 1·4984; a portion (0·50 g.), heated on a steam-bath for 4 hr. with hydrochloric–hydrobromic acid (2·0 ml.), yielded 2 : 4-dimethylphenylacetic acid (0·19 g.), m. p. 100°, and the acid *A* (5 mg.), m. p. 202—203°. Attempts to isolate the ketone (IV), as such and as derivatives, from the syrup did not succeed.

(*e*) A stirred suspension of (±)-*trans*-pinonic acid (3·0 g.) in hydrochloric–hydrobromic acid (3·0 ml.) was immersed in a thermostat bath at 48°. After 10 min. the clear solution was poured into water (100 ml.) and aqueous ammonia (*d* 0·88; 10 ml.) was added; extraction

yielded the ketone (III) (0·78 g.), and, by extraction of the aqueous liquid after acidification with hydrochloric acid, pinonic acid (1·88 g.) was recovered.

Reaction in Phosphoric Acid.—(±)-*trans*-Pinonic acid (80 g.) and phosphoric acid (200 g.), in a distillation flask, were immersed in an oil-bath previously heated to 180°; the pinonic acid dissolved; thereafter, at 150°, evolution of carbon dioxide and separation of an oil commenced; the temperature of the mixture rose to 165°, heating of the oil-bath having been discontinued latterly, and an oil and water distilled. Water (150 ml.) was added to the flask, and the contents were distilled in steam. The aqueous distillate (*B*) was separated from the oil (*C*), and the aqueous phosphoric acid (*D*) was decanted from a resin (*E*).

[In the account below, (VII) and (XI) refer respectively to (impure) specimens of 2 : 4-dimethylphenylacetic acid and 2-hydroxy-2 : 4-dimethyl*cyclo*hexylacetic lactone.]

The distillate *B* (4 l.) was repeatedly extracted (total solvent, 400 ml.); the extract yielded an oil (7·5 g.), which was washed in methylene chloride (25 ml.) with aqueous sodium carbonate. The latter on acidification with dilute sulphuric acid gave (VII) (1·5 g.), m. p. 98°. The solution was evaporated and the product boiled under reflux for 2 hr. with ethanolic 0·5N-potassium hydroxide (75 ml.). After dilution with water (100 ml.) and extraction of non-hydrolysable material (0·1 g.), the alkaline solution was acidified and extracted; the lactone (XI) (5·6 g.) was obtained.

The oil *C* was washed in methylene chloride with aqueous sodium carbonate and separated through a short distillation column into volatile and involatile portions. The former was kept over, then distilled from, sodium, and yielded a colourless distillate (F_2) (11·8 g.), b. p. 150—170°, n_D^{25} 1·4780. Treatment of the involatile portion with ethanolic potassium hydroxide (50 ml.), as above, gave a viscous non-hydrolysable oil (*G*) (5·8 g.) and (XI) (1·3 g.).

The aqueous material *D*, on treatment as for *B*, gave (VII) (0·2 g.), m. p. 101°.

The resin *E* was washed in methylene chloride with water, recovered, and heated at 100°/0·2 mm. for 6 hr. in a sublimation-apparatus; solution of the sublimate in methylene chloride and extraction with aqueous sodium carbonate effected separation into a neutral gum (1·0 g.) and (VII) (0·8 g.), m. p. 101—102°. A soft, brown, clear resin (28·9 g.) remained in the apparatus.

Characterisation of products. Specimens of (VII) were combined and recrystallised from *cyclo*hexane, yielding 2 : 4-dimethylphenylacetic acid (1·97 g.), m. p. 101—103°, and, after recrystallisation from water, m. p. and mixed m. p. 105°. A 1 : 1 mixture of (±)-*trans*-pinonic acid (m. p. 105—105·5°) and 2 : 4-dimethylphenylacetic acid had m. p. 77—80°.

The material (3·4 g.) from combination and distillation of specimens of (XI) gave, on redistillation, 2-*hydroxy*-2 : 4-*dimethyl*cyclo*hexylacetic lactone*, b. p. 102—103°/0·7 mm., n_D^{25} 1·4693 (Found: C, 71·5; H, 9·55%; equiv., 169·2. $C_{10}H_{16}O_2$ requires C, 71·45; H, 9·55%; equiv., 168·2). The lactone (0·091 g.), hydrochloric acid (0·17 ml.), and bromine (0·061 g.) were heated at 100° for 1 hr. in a sealed tube. The organic acidic product, separated by aqueous sodium carbonate, on being heated for 2½ hr. at 100°/0·1 mm., gave a sublimate (0·049 g.) which on recrystallisation yielded 2 : 4-dimethylphenylacetic acid, m. p. and mixed m. p. 103°.

The oil *G*, on redistillation, gave an unsaturated hydrocarbon fraction, b. p. 125—128°/3·5 mm., n_D^{25} 1·5084 (Found: C, 88·1; H, 11·6%).

The ψ-cumene contents of the hydrocarbon F_2 and similar fractions were estimated by the following nitration procedure. The hydrocarbon (0·290 g.) was added dropwise with shaking to a cooled mixture of nitric acid (*d* 1·42; 2·0 ml.) and sulphuric acid (3·0 ml.). After being heated in a steam-bath for 10 min., with occasional shaking, the mixture was poured into water (100 ml.). The product was collected, washed with water (100 ml.), then with ethanol (4 ml.), and dried *in vacuo*; the yield and, after one recrystallisation from ethanol where necessary, the m. p., and m. p. when mixed with 3 : 5 : 6-trinitro-ψ-cumene having m. p. 188—189°, were determined. The m. p.s and mixed m. p.s of the specimens lay in the ranges 183—185° and 185—187°. In a control experiment ψ-cumene, b. p. 167—169°, n_D^{25} 1·5020, gave 60% of the nitro-compound; F_2 yielded 23%.

The volatile hydrocarbon mixture from a preceding decomposition, F_1, b. p. 149—167°, n_D^{25} 1·4811, was investigated as follows. (i) A portion was separated into fractions. The lower-boiling showed strong unsaturation to bromine in carbon tetrachloride. The fraction of b. p. 165—166°, n_D^{25} 1·4967, gave 49% of trinitro-ψ-cumene, which was recrystallised to constant m. p. 188°, mixed m. p. 188—189°. Fractions of b. p. 155·5—157°, n_D^{25} 1·4699, and b. p. 153—154°, n_D^{25} 1·4650, each gave 5%. The fraction of b. p. 149—150°, n_D^{25} 1·4583 (0·38 g.),

was boiled for 5 hr. with 7% palladised charcoal (0·039 g.). The product, b. p. 154—170°, n_D^{25} 1·4683, gave a 28% yield of trinitro-*ψ*-cumene. For the fraction of b. p. 151—153°, n_D^{25} 1·4587, there was found: C, 87·65; H, 12·45 (Calc. for C_9H_{16}: C, 87·0; H, 13·0. Calc. for C_9H_{12}: C, 89·85; H, 10·05%).

(ii) Ozonolysis in acetic acid gave no identified product. This finding may be due to the formation of stable polymeric ozonides similar to those obtained by Criegee and his co-workers from 1 : 2-dimethyl*cyclo*hexene.[5]

(iii) Material F_1 and the following olefins (0·004 mole) were hydrogenated in methanol (20 ml.) in the presence of platinum (from, for each run, 15 mg. of Adams platinic oxide) at slightly above atmospheric pressure, with the following absorptions: *cyclo*hexene 86% in 20 min. at 23°; 1-methyl*cyclo*hexene 27% in 20 min., 49% in 120 min. at 23°; 1 : 2-dimethyl*cyclo*hexene 3% in 20 min., 5% in 120 min. at 21°; material F_1 (assumed for calculation to be half 1 : 2 : 4-trimethyl*cyclo*hexene and half *ψ*-cumene) 6% in 20 min., 8% in 120 min. at 21°.

β-n-*Butyl-γγ-dimethyl-γ-butyrolactone.*—The (±)-ketone (III) (12·5 g.) was dissolved in a warm solution of potassium hydroxide (12·5 g.) in diethylene glycol (90 ml.), and aqueous hydrazine hydrate (*d* 1·013; 5 ml.) was added; the whole was boiled under reflux for 1½ hr., raised to 205° while distillation was allowed to proceed, then kept under reflux at this temperature for 4½ hr. After cooling, water (150 ml.) was added and neutral material (0·6 g.) removed by extraction. The alkaline liquid was acidified with dilute sulphuric acid, then repeatedly extracted; the extract was washed with water, and dried (K_2CO_3). It yielded an oil (6·5 g.), b. p. 136—141°/13 mm., repeated fractionation of which gave β-n-*butyl-γγ-dimethyl-γ-butyrolactone* (1·1 g.), b. p. 99·5°/1·2 mm., n_D^{25} 1·4470 (Found: C, 70·3; H, 10·6%; equiv., 168·6. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·7%; equiv., 170·2).

Decarboxylations.—The compound (240 mg.) and phosphoric acid (1·0 ml.) were placed in a 5 ml. flask attached, *via* a short reflux condenser, to an oil-filled gas-burette. The flask was immersed in an oil-thermostat at 160°; periodically it was removed and allowed to cool, the increase in gas-volume was observed, and the percentage decarboxylation calculated.

Compound	Decarboxylation (%) in 5 min.	10 min.	30 min.
Pinonic acid	54	59	60
2-Hydroxy-2 : 4-dimethyl*cyclo*hexylacetic lactone	—	16	39
β-n-Butyl-*γγ*-dimethyl-*γ*-butyrolactone	—	1	5

2-Hydroxy-2 : 4-dimethyl*cyclo*hexylacetic lactone (3·25 g.), in solution in phosphoric acid (13 ml.), was heated for 3 hr. under reflux at 160°; an oil separated. The mixture was cooled, then diluted with water, and the oil extracted with ether; repeated fractionation, and drying with sodium, yielded a hydrocarbon, probably 1 : 2 : 4-*trimethyl*cyclo*hexene* (0·25 g.), b. p. 144—145°, n_D^{25} 1·4430 (Found: C, 86·75; H, 13·55. C_9H_{16} requires C, 87·0; H, 13·0%).

2 : 4-Dimethylphenylacetic acid (1·00 g.) was heated with phosphoric acid (10 ml.) for 1 hr. at 160—170°; it (0·95 g.) was recovered, having m. p. 104—105°.

2-Hydroxy-2 : 4-dimethyl*cyclo*hexylacetic lactone and β-*n*-butyl-*γγ*-dimethyl-*γ*-butyrolactone differ notably in their rates of hydrolysis: for complete hydrolysis the former lactone required 2 hours' boiling under reflux with ethanolic 0·5N-potassium hydroxide, whereas the latter was completely hydrolysed in 30 min. at room temperature with this reagent.

The olefins used for determination of hydrogenation rates were distilled from sodium. *cyclo*Hexene had b. p. 81·5—82°, n_D^{25} 1·4440; 1-methyl*cyclo*hexene, prepared by dehydration of a mixture of *cis*- and *trans*-2-methyl*cyclo*hexanol with phosphoric acid, had b. p. 109—109·5°, n_D^{20} 1·4484, n_D^{25} 1·4458; 1 : 2-dimethyl*cyclo*hexene, prepared by slow distillation of a mixture of *cis*- and *trans*-1 : 2-dimethyl*cyclo*hexanol with iodine, had b. p. 136·5—137°, n_D^{25} 1·4574.

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[5] Criegee and Lohaus, *Chem. Ber.*, 1953, **86**, 1; Criegee, *Annalen*, 1953, **583**, 1.

XUM

646. *Infrared Spectra and the Polymorphism of Glycerides. Part IV.*[1] *Myristopalmitins and Myristostearins.*

By D. Chapman.

The polymorphism of some myristo-palmitins and -stearins has been investigated by infrared spectroscopy between 1800 and 650 cm.$^{-1}$, and data on the transitions have been obtained.

This paper extends our infrared spectroscopic studies [1,2] to the polymorphism of 2-myristo-distearin, 1-stearodimyristin, 2-myristodipalmitin, and 1-palmitodimyristin. These glycerides have been previously examined by Malkin *et al.*[3] and by Lutton *et al.*[4] who used thermal and *X*-ray techniques. Of these glycerides, the first is of particular interest since, unlike most other saturated triglycerides which have only three polymorphic forms, it is reported to have an additional fourth form [4] (designated β′-4). Malkin *et al.*[3] did not report this form, although they noted four melting points.

Experimental

2-Myristo-distearin and -dipalmitin, and 1-stearo- and 1-palmito-dimyristin, were prepared (by Dr. W. T. Weller of this laboratory) by refluxing 1 : 3-distearin, 1 : 3-dipalmitin, 1-monostearin, and 1-monopalmitin respectively with a small excess of myristoyl chloride (prepared from myristic acid, setting point 53—59°) in purified chloroform–pyridine for some hours. They were finally recrystallised a number of times from ethanol and acetone.

The infrared spectrometer was a Grubb-Parsons S.3 double-beam spectrometer with a rock-salt prism. The spectra were obtained between 1800 and 650 cm.$^{-1}$ with capillary thicknesses of the glycerides between rock-salt flats. A cell which could be heated or cooled was used for investigating the polymorphic transitions, and to obtain the spectra of the glycerides in the liquid state. Rapid scanning of parts of the spectrum (in particular the 1250 and 720 cm.$^{-1}$ regions) during heating or cooling disclosed the transition temperatures (which are in good agreement with those given by Lutton *et al.*[4]); these were confirmed by capillary-tube methods. The forms obtained by crystallisation from solvent were examined both as Nujol mulls and in KCl discs: *X*-ray data on all the polymorphic forms were also obtained, and are in good agreement with those given by Lutton *et al.*[4]

The α_L-forms were obtained by quenching the melt to 0°, the β'_L-forms by warming the α_L-form to the transition temperature and also by rapid crystallisation from light petroleum or alcohol; the β_L-forms were obtained by heating the β'_L-forms to the transition temperature or by keeping them at this temperature for some time, and also by slow crystallisation from, *e.g.*, acetone.

Discussion

The polymorphic forms of the triglycerides previously examined by the infrared spectroscopic method have given spectra which can be classified into three main types.[1] Whilst the spectra within a certain type vary slightly from one glyceride to another, notably in the 1250 cm.$^{-1}$ region, each type has a certain "family" appearance. This supports a similar classification of these glycerides [5] on the basis of their *X*-ray short spacings, such a classification being possible because of the general constancy of packing of the hydrocarbon chains in the different forms. Forms designated [1] α_L are considered to have hexagonal packed chains; β'_L-forms probably have orthorhombic packed chains, and β_L triclinic packed chains.

The spectra of the myristo-palmitins and -stearins show that the polymorphic forms of these glycerides (apart from the higher intermediate form of 2-myristodistearin) fit this classification. The β_L-forms show a single band at 718 cm.$^{-1}$ and a prominent band at

[1] Part III, Chapman, *J.*, 1957, 2715.
[2] Chapman, *J.*, 1956, 55, 2522.
[3] Malkin and Meara, *J.*, 1939, 103; Carter and Malkin, *J.*, 1939, 577.
[4] Jackson and Lutton, *J. Amer. Chem. Soc.*, 1949, **71**, 1976.
[5] Lutton, *J. Amer. Oil Chemists' Soc.*, 1950, **27**, 276.

XUM

890 cm.$^{-1}$, similar to those of other saturated glycerides previously designated β_L, *e.g.*, tristearin. (This is despite the fact that the stable β_L-forms of 2-myristodipalmitin and 1-palmitodimyristin are of double-chain-length structure whilst the β_L-forms of the two stearo-analogues have the triple-chain-length structure.) The α_L-forms show a single band at 720 cm.$^{-1}$, whilst the β'_L-forms show a doublet at 726 and 719 cm.$^{-1}$. These also are similar to those of the corresponding forms of other saturated triglycerides.[1,2]

FIG. 1.

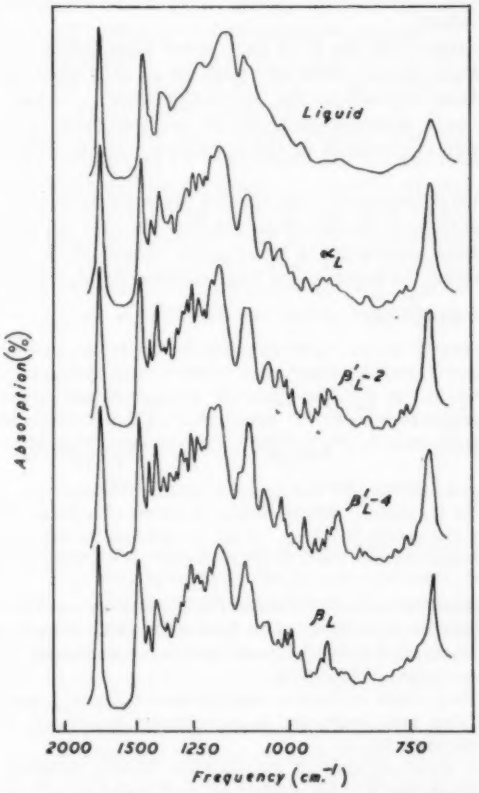


FIG. 2.

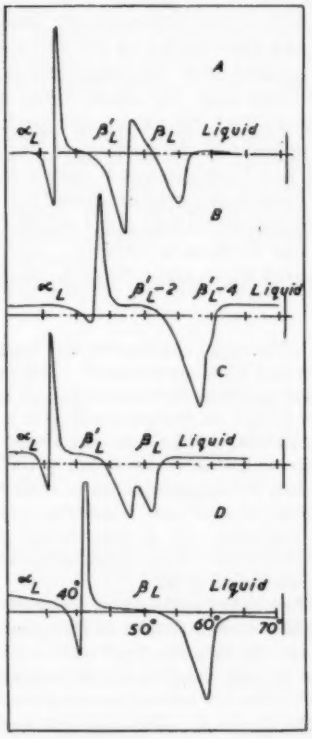


FIG. 1. *Infrared spectra of polymorphic forms of 2-myristodistearin.*

FIG. 2. *Differential heating curves of (A) 1-stearodimyristin, (B) 2-myristodistearin, (C) 1-palmitodimyristin, and (D) 2-myristodipalmitin.*

There are other differences between the spectra of the polymorphic forms of each glyceride, notably in the intensity patterns in the 1250 cm.$^{-1}$ region. The spectra of each of the β_L-forms of these glycerides show small differences from each other in this region. The major bands are similar to those observed in other triglycerides, *e.g.*, the β_L- forms have a strong band between 1730 and 1740 cm.$^{-1}$ and two strong bands near 1170—1180 and 1100 cm.$^{-1}$.

Owing to the rapidity of the intermediate transition in 2-myristodipalmitin, only the spectra of two forms α_L and β_L could be obtained, although there was slight evidence for the intermediate transition, *e.g.*, a fleeting asymmetrical broadening of the 720 cm.$^{-1}$ band before the transition to the β_L-form. (This can be compared with the behaviour of the homologous glyceride, 2-palmitodistearin, where only two forms were observed.[3])

The spectrum of the higher-melting intermediate form of 2-myristodistearin (see Fig. 1) is different from that of the β′-2 form. One outstanding feature is that a band at 1193 cm.$^{-1}$ becomes as strong as that at 1174 cm.$^{-1}$. The spectrum also shows that the band at 720 cm.$^{-1}$ is asymmetrically broadened on the high-frequency side, indicating the presence of a doublet not clearly resolved; and a strong band at 886 cm.$^{-1}$ is present. When further heated, this form melts (when held at 50—60° for some time it changes into the stable β-3 form). Lutton [5] designates the intermediate form as β'_L-4. The long spacing is greater than that of the β′-2 form and the short spacings also differ. This form, however, fits Lutton's *X*-ray short-spacing classification.

Since the doublet in the 720 cm.$^{-1}$ region for the β'_L-4 form is not clearly resolved we may predict that the interchain distances in this form are perhaps greater than in the β'_L-2 forms since the extent of the splitting depends on the interaction forces. It may be, however, that the chains are packed only approximately in the orthorhombic manner. The relation of the packing of long-chain compounds to the appearance of the 720 cm.$^{-1}$ band has been discussed elsewhere.[6]

Whilst four forms are found for 2-myristodistearin the spectra are consistent with the conclusions of Lutton *et al.*[4] rather than those of Malkin *et al.*[3], in that they do not suggest that one of them is vitreous. Deductions analogous to those given previously for other saturated triglycerides [1] can be made about the spectra and their relation to crystal forms.

Appendix

A differential calorimeter has been recently shown to be valuable for studying commercial fats [7a] and pure glycerides.[7b] The present glycerides have been studied with this apparatus and the resultant heating curves are shown in Fig. 2. The glyceride was melted and quenched in ice, placed in the calorimeter at a temperature some 10° below that of the lowest-melting form, and heated at a rate of 1·1° per minute until finally molten. (The temperatures given on the curves are accurate within ±1·5°.)

When 1-stearodimyristin is heated, some melting of the α_L-form occurs, followed by rapid evolution of heat and transition into the β'_L-form. When further heated, this form melts, gives out heat, and is transformed into the stable β_L-form. This in turn melts and finally becomes liquid. Thus three forms are observed and there is no evidence for an intermediate form having m. p. 52°.

When 2-myristodistearin is heated, a small amount of melting of the α_L-form occurs, followed by rapid evolution of heat and transition into the β'_L-2 form. This form melts and is transformed very rapidly into the β'_L-4 form which when further heated melts and becomes liquid. (The stable β_L-form is obtained only after some hours at 50—60°.)

With the 1-palmitodistearin, some melting of the α_L-form occurs, followed by rapid transition into the β'_L-form. When further heated this form melts and is transformed into the β_L-form. On being further heated this melts and becomes liquid.

When 2-myristodipalmitin is heated, some melting of the α_L-form occurs, followed by evolution of heat and transition into the stable β_L-form. This in turn melts and becomes liquid. No evidence for a β'_L-form is observed.

Malkin [8] has recently emphasised the use of heating and cooling curves for the study of the polymorphism of glycerides. It is evident that the differential calorimeter will play an important rôle in many future studies.

I thank Mr. H. Lavery and Dr. C. R. McCowan of this Department for allowing me the use of their differential calorimeter. I also thank the Directors of Unilever Limited for permission to publish this work.

Research Department, Unilever Limited,
Port Sunlight, Cheshire. [*Received, January 29th,* 1958.]

[6] Chapman, *J.*, 1957, 4489.
[7] (*a*) Hannewijk and Haighton, (*b*) Lavery, *J. Amer. Oil Chemists' Soc.*, in the press.
[8] Malkin, "Progress in the Chemistry of Fats and other Lipids," Vol. II, Pergamon Press Ltd., London, 1954.

XUM

647. *The Structure of Bornesitol.*

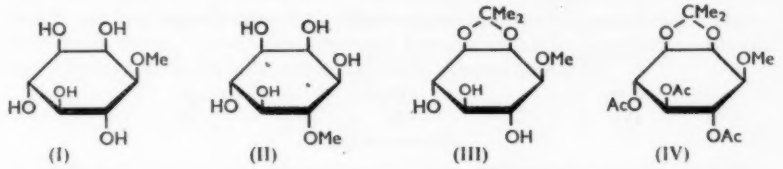
By Shlomo Bien and David Ginsburg.

(−)-Bornesitol isolated from *Lithospermum ruderale* L. has been proved by degradative experiments to possess structure (I).

Optically active bornesitol has been isolated from a number of natural sources (see Angyal *et al.* for a recent review [1]). The lævorotatory isomer was isolated in our laboratory in about 1% yield from *Lithospermum ruderale* L.[2] and was shown to be a monomethyl ether of *myo*inositol. Since the compound was optically active it is possible to formulate its structure only as (I) or as (II). Degradative work was undertaken in order to select the correct structure unequivocally.

Notwithstanding the results obtained with our product which "has a similar ionophoretic mobility to (+)-bornesitol but it responded to the detection spray (ammoniacal silver nitrate) slightly differently,"[3] and the elegant correlation of dambonitol and racemic bornesitol [1] which appeared while our work was in progress, this communication details the first direct unequivocal proof of the structure of the natural product. The formulation of bornesitol as (I) by previous workers [1,3] has been proved correct.

Demethylation of (−)-bornesitol, $[\alpha]_D^{18}$ −32·05°, was effected by hot concentrated hydriodic acid; *myo*inositol was obtained in 95% yield.



(−)-Bornesitol was converted into 1-*O*-methyl-2 : 3-*O*-*iso*propylidene*myo*inositol (III) by treatment with acetone in the presence of acetic acid and zinc chloride under anhydrous conditions. This derivative existed in two dimorphic forms, m. p. 60—62° and 112—114°, respectively, both of which on acetylation in pyridine solution afforded 4 : 5 : 6-tri-*O*-acetyl-1-*O*-methyl-2 : 3-*O*-*iso*propylidene*myo*inositol (IV). The derivative (III) was accompanied by a small quantity of di*iso*propylidene compound which was acetylated under similar conditions.

In order to determine whether inversion of configuration occurred during formation of the di*iso*propylidene derivative, it and the mono*iso*propylidene compound were treated separately with boron trifluoride–ether complex in methanol. In each case, (−)-bornesitol was reconstituted in high yield.

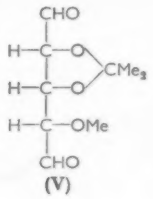
Angyal and Macdonald [4] discussed formation of a tri*iso*propylidene derivative of *epi*inositol and of (−)-inositol in which one *iso*propylidene group must bridge a pair of *trans*-hydroxyl groups, in terms of the conformations of the molecule. It has now been shown that when one equatorial methoxyl group is present in a *myo*inositol derivative, the presence of *one iso*propylidene group bridging a pair of adjacent *cis*-hydroxyl group exerts sufficient influence on the conformation of the molecule to enable a second such group to bridge a pair of adjacent *trans*-hydroxyl groups. However, the positions of the *iso*-propylidene groups in this substance have not been determined.

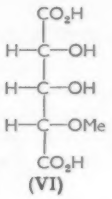
The mono*iso*propylidene derivative (III) was oxidised with lead tetra-acetate in dry

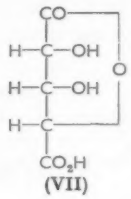
[1] Angyal, Gilham, and Macdonald, *J.*, 1957, 1417.
[2] Gorman, Bien, and Ginsburg, *Bull. Res. Council Israel*, 1956, **5**, *A*, 253.
[3] Dr. A. B. Foster, personal communication, March 1st, 1956; cf. Foster and Stacey, *Chem. and Ind.*, 1953, 279.
[4] Angyal and Macdonald, *J.*, 1952, 686.

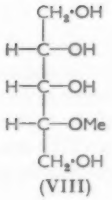
XUM

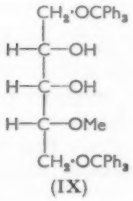
chloroform, affording the syrupy dialdehyde (V). Oxidation of this with bromine-water in the presence of strontium carbonate [5] afforded the strontium salt of the corresponding diacid (VI), which after suitable working up including a demethylation step (see p. 3191) gave a syrup showing the expected infrared absorption for a lactone-acid. Now, if bornesitol possesses structure (I), the lactone-acid should be the γ-lactone of *ribo*trihydroxyglutaric acid,[6] whilst if it possesses structure (II) the γ-lactone of talomucic acid [7] would be expected to be formed at this stage of the degradative procedure. An authentic specimen of the γ-lactone of *ribo*trihydroxyglutaric acid (VII) was prepared from D-(−)-ribose [8] [it does not matter which optical isomer of ribose is used as starting material because the acid (VII) is optically inactive]. The authentic specimen (VII) had m. p. 168—170°. Although the infrared spectra of the authentic sample and of the syrup obtained from the natural product were virtually superimposable [these included bands at 1785 (γ-lactone) and 1735 cm.$^{-1}$ (CO_2H) in KBr], the spectrum of the latter included an additional band at 1630 cm.$^{-1}$, indicating the presence of small quantities of unsaturated impurities. Even seeding of the syrup resulting from the natural product with a small amount of crystalline authentic specimen did not lead to its crystallisation. We therefore turned our attention to an alternative structural proof, namely, to reduction rather than oxidation of the dialdehyde (V).

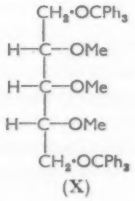

(V)

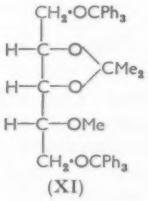

(VI)


(VII)


(VIII)


(IX)


(X)


(XI)

The dialdehyde (V) was reduced with sodium borohydride in methanol solution, and the resulting tetra-alcohol (VIII) was treated with triphenylmethyl chloride in pyridine, affording the ditrityl derivative (IX) accompanied by some monotrityl derivative. The ditrityl compound (IX) was methylated several times with dimethyl sulphate in the presence of sodium hydroxide, giving the trimethyl ditrityl ether (X) and a dimethyl ditrityl ether which could be one of two isomers.

In parallel, ribitol obtained by sodium borohydride reduction of ribose similarly yielded a mixture of the trimethyl ether (X) and a dimethyl ether. Since these two compounds did not depress the melting points of the corresponding ones obtained from natural (−)-bornesitol and since the corresponding infrared spectra were superimposable, it is clear that bornesitol possesses structure (I) and not (II). No effort was expended in working out conditions for complete methylation of the ditrityl compound (IX), since incomplete reaction in both of the above routes afforded two, rather than one, sample for comparison.

[5] Iwadare, *Bull. Chem. Soc. Japan*, 1941, **16**, 40.
[6] Fischer and Piloty, *Ber.*, 1891, **24**, 4222.
[7] Steiger and Reichstein, *Helv. Chim. Acta*, 1936, **19**, 195.
[8] Levene and Jacobs, *Ber.*, 1909, **42**, 3248.

Yet another route was employed to prove the structure of the ether (X). 2 : 3 : 4-Tri-*O*-methylribose [9] was reduced with sodium borohydride and treated with triphenylmethyl chloride, again affording 2 : 3 : 4-tri-*O*-methyl-1 : 5-di-*O*-tritylribitol (X), identical with the substance obtained by degradation of (−)-bornesitol.

The structure of the dimethyl ditrityl ether was proved as follows. After treatment with acid the resulting dimethylribitol in aqueous solution was treated with sodium periodate: [10] there was no reaction, as was the case also with the trimethyl ditrityl ether. Ribitol and 1 : 5-di-*O*-tritylribitol under these conditions gave, of course, a positive test. The substance in question is therefore formulated as 2 : 4-di-*O*-methyl-1 : 5-di-*O*-tritylribitol.

Di-*O*-tritylribitol has been described previously, and called ditrityladonitol,[11] as a compound having m. p. 141—145°. In our hands, during working up of the ribitol tritylation mixture, crystallisation of a mixture of the mono- and the di-trityl derivative afforded a mixture having m. p. 138—146°, but further crystallisation afforded the pure monotrityl derivative, m. p. 141·5° and the pure ditrityl derivative, m. p. 156° (see p. 3194). It therefore appears that the previously reported ditrityl derivative [11] was, in fact, a mixture. Valentin [11] also reported long melting ranges for other trityl derivatives which he prepared.

By inspection of formula (VIII) and that of the corresponding isomer of the arabitol configuration, it is clear that exhaustive methylation of the former would be expected to give an optically inactive pentamethyl ether whilst the corresponding derivative of the latter should exhibit optical activity. However, since either pentamethyl ether would most likely be a syrup, the above approach using tritylation in order to obtain solid derivatives to effect the structural proof, appeared more reasonable.

Experimental

(−)-*Bornesitol.*—This product crystallised in large transparent rhombs from a boiling methanolic extract of *Lithospermum ruderale* L. after the plant has been defatted with light petroleum; it had m. p. 205—206° (from methanol or aqueous acetone), $[\alpha]_D^{18}$ −32·05° (*c* 3·5 in H_2O) (Found: C, 43·2; H, 7·2; O, 49·7; OMe, 16·5. Calc. for $C_7H_{14}O_6$: C, 43·3; H, 7·3; O, 49·4; OMe, 15·9%).

Demethylation.—(−)-Bornesitol (1 g.) was heated under reflux for 5 min. with 47% hydriodic acid (3 ml.). After cooling, propan-1-ol was added. The product (0·88 g., 95%) had m. p. 225—227° (from aqueous propan-2-ol) and did not depress the m. p. of authentic *myo*inositol. The infrared spectra of the product and its hexa-acetate, m. p. 213° (from methanol), were identical with those of *myo*inositol and its hexa-acetate, respectively.

(−)-*Bornesitol Penta-acetate.*—A solution of (−)-bornesitol (0·1 g.) in pyridine (3 ml.) and acetic anhydride (3 ml.) was warmed on the steam-bath for 5 hr. Evaporation to dryness and crystallisation from methanol afforded the penta-acetate, m. p. 142—143° (0·09 g., 43%). A second m. p., 157°, was observed in some samples of this substance (Found: C, 50·0; H, 6·0; O, 43·55; Ac, 54·1. Calc. for $C_{17}H_{24}O_{11}$: C, 50·5; H, 6·0; O, 43·5; Ac, 53·2%). Plouvier [12] reports m. p. 203—204° for (−)-bornesitol isolated from *Lathrus vernus* Bernh., $[\alpha]_D$ −32°, and double m. p. 142° and 157° for the penta-acetate. The infrared spectrum of our product was identical with that of (±)-bornesitol penta-acetate kindly provided by Dr. L. Anderson.[13]

4 : 5 : 6-*Tri*-O-*acetyl*-1-O-*methyl*-2 : 3-O-iso*propylidene*myo*inositol.*—Dry finely powdered (−)-bornesitol (1·25 g.) and anhydrous zinc chloride (10 g.) were heated with dry acetone (100 ml.) and glacial acetic acid (10 ml.) under reflux for 6—8 hr. The colourless mixture slowly became yellow. Next morning, dry pyridine (45 ml.) was added and the mixture was refrigerated for 4 hr. The precipitated zinc chloride–pyridine complex [14] was removed by

[9] Levene and Tipson, *J. Biol. Chem.*, 1931, **93**, 623.
[10] Feigl, "Spot Tests," 4th edn., Vol. II, p. 102, Elsevier, Amsterdam, 1954.
[11] Valentin, *Coll. Czech. Chem. Comm.*, 1931, **3**, 499 (through *Chem. Abs.*, 1932, **26**, 1577).
[12] Plouvier, *Compt. rend.*, 1955, **241**, 983.
[13] Anderson and Landel, *J. Amer. Chem. Soc.*, 1954, **76**, 6130.
[14] Posternak, *Helv. Chim. Acta*, 1952, **35**, 52.

XUM

filtration and washed with a little cold acetone. After concentration of the mother-liquor under reduced pressure to about one-half of its volume the residual complex was again removed. Finally all of the solvents were evaporated under reduced pressure, acetic anhydride (15 ml.) and pyridine (10 ml.) were added, and the mixture was set aside overnight at room temperature. After dilution with chloroform (80 ml.) the solution was washed with ice-cold sodium hydrogen carbonate solution and then with water. The chloroform layer was dried (Na_2SO_4), and the solvents were removed at the water-pump, affording a crude semicrystalline mass (1·9 g.). Crystallisation from ethyl acetate afforded needles of the *monoisopropylidene derivative triacetate*, m. p. 157° (0·85 g.). Two recrystallisations (charcoal) raised the m. p. to 158—159°; $[\alpha]_D^{18}$ was +9·0° (*c* 1·4 in $CHCl_3$) (Found: C, 53·4; H, 6·8; O, 40·25. $C_{16}H_{24}O_9$ requires C, 53·3; H, 6·7; O, 40·0%).

Working up of the mother liquor was difficult as it contained three different acetates. Some success was achieved by evaporation of the mother-liquor to dryness and addition of absolute methanol (12 ml.) and sodium methoxide (0·1 ml. of N-solution) [15] to effect deacetylation of the products. After 24 hr. rhombs of (−)-bornesitol were deposited. The resulting mother liquor was evaporated to dryness and the residue was chromatographed on a cellulose powder column (Whatman standard grade) with acetone–water (4 : 1) as the moving phase and methyl orange to indicate the solvent front. Fractions (5 ml.) were collected. From a residue of 0·36 g. the major portion was collected in the first 8 fractions (0·34 g.). Fractions 1—3 yielded a semi-solid product whilst fractions 4—8 gave a syrup. The former gave, after recrystallisation from a very dilute solution to avoid formation of a gelatinous product, the *diisopropylidene derivative*, m. p. 138—139° (from methyl*cyclo*hexane) (Found: C, 56·05; H, 8·0; O, 35·2; OMe, 11·5. $C_{13}H_{22}O_6$ requires C, 56·9; H, 8·1; O, 35·0; OMe, 11·3%).

The *monoacetate* of the di*iso*propylidene derivative was obtained from this product (40 mg.) by acetic anhydride (3 ml.) in pyridine (3 ml.); it had m. p. 174° (from methyl*cyclo*hexane) (Found: C, 56·3; H, 7·7; OMe, 9·9; Ac, 14·4. $C_{15}H_{24}O_7$ requires C, 56·95; H, 7·65; OMe, 9·8; Ac, 13·6%).

To the di*iso*propylidene derivative (40 mg.) in methanol (1 ml.) boron trifluoride–ether complex (3 drops) was added. Crystals (23 mg.) deposited overnight were (−)-bornesitol (mixed m. p.; penta-acetate).

The syrup in fractions 4—8 (see above) was triturated with ethyl acetate. The *mono*iso*propylidene derivative* crystallised from this solvent in two dimorphic forms, m. p. 60—62° and m. p. 112—114°, the latter being formed after long storage of a dilute solution (Found: C, 51·5; H, 8·0; O, 40·55. $C_{10}H_{18}O_6$ requires C, 51·3; H, 7·75; O, 41·0%). The infrared spectra of both forms (in $CHCl_3$) were identical.

Acetic anhydride in pyridine afforded the triacetate, m. p. 158°, identical with the product described above. Alternatively, deacetylation of the mono*iso*propylidene derivative triacetate with sodium methoxide in methanol afforded either of the dimorphic forms of the mono*iso*propylidene derivative. The crude mono*iso*propylidene derivative usually obtained as a syrup was sufficiently pure for further transformations.

Deacetylation could also be effected by dissolving the compound (0·2 g.) in dry methanol (15 ml.) and saturating the solution (at −10°) with dry ammonia. The solution was kept at 0° for 24 hr. Evaporation gave a syrup from which acetamide was sublimed at 80°/0·01 mm. The resulting syrup (120 mg.) crystallised from ethyl acetate and had m. p. 113°.

Lead Tetra-acetate Oxidation.—To a solution of the crude mono*iso*propylidene derivative (300 mg.) in dry chloroform (5 ml.) was added anhydrous potassium carbonate (0·7 g.) followed, portionwise, by lead tetra-acetate (1·32 g.) with vigorous stirring. The reaction was complete after about 2 hr. (starch–iodide paper). The crystals of lead acetate were removed and washed with chloroform and the combined chloroform solutions were evaporated at 40° at the water-pump. The residue was triturated with dry ether, and additional precipitate was removed. Evaporation and trituration with ether was repeated several times, finally affording a thick syrupy residue of the dialdehyde (V) (240 mg.), $\nu_{max.}$ 1735 cm.$^{-1}$ (saturated C=O).

Reduction of the Dialdehyde.—Small portions of sodium borohydride (120 mg.) were added to a solution of the syrupy dialdehyde (240 mg.) in methanol (5 ml.); the vigorous reaction was moderated by cooling in an ice-bath. After being kept overnight, the mixture was acidified with hydrochloric acid and concentrated, methanol being added repeatedly during the concentration. The product was separated from inorganic salts by several extractions with

[15] Zemplen and Pacsu, *Ber.*, 1929, **62**, 1613.

propan-2-ol. Evaporation of the latter gave a syrup (220 mg.) which showed no C=O absorption in its infrared spectrum (in KBr) and exhibited only a strong band in 3350 cm.$^{-1}$ (OH).

Tritylation and Methylation of Sodium Borohydride Reduction Product.—Triphenylmethyl chloride (0·7 g.) was added to a solution of the above syrupy reduction product (200 mg.) in dry pyridine (2 ml.). The mixture was kept at room temperature for 3 days under anhydrous conditions. The mixture was filtrated from a small amount of precipitate and was diluted with chloroform (30 ml.). The chloroform solution was washed several times with ice-cold sodium hydrogen sulphate solution (5%) and then with water. The chloroform layer was dried (sodium sulphate) and the solvent was removed at the water pump, giving a syrupy residue (730 mg.). The latter was dissolved in benzene (2 ml.) and light petroleum (2 ml.) and was chromatographed on alumina (30 g.; Fisher). Fractions of 25 ml. were taken. Elution with light petroleum gave a semi-solid (*ca.* 60 mg.), m. p. 181° (from propan-2-ol). Infrared absorption showed no free hydroxyl group. This compound is probably 2-*O*-methyl-3 : 4-*O*-*iso*propylidene-1 : 5-di-*O*-tritylribitol (XI) which survived acid hydrolysis after the sodium borohydride reduction.

Elution was continued with benzene, benzene-chloroform and finally with pure chloroform giving oily residues in the various fractions (*ca.* 120 mg.). Infrared absorption (in $CHCl_3$) indicated the presence of trityl groups (strong phenyl absorption at 1600 and 1490 cm.$^{-1}$) and free OH groups (3500 cm.$^{-1}$). Among these fractions [elution with benzene–chloroform (70 : 30)], triphenylmethanol was isolated (350 mg.). All the oily fractions, except those containing triphenylmethanol, were combined and dissolved in acetone (8 ml.). 30% Aqueous sodium hydroxide (5 ml.) and dimethyl sulphate (1·8 ml.) in acetone (3 ml.) were alternately added dropwise with vigorous stirring, so that the solution remained alkaline throughout, the temperature being maintained at 45°. This addition was repeated twice more and a distillation head was attached to the reaction flask; the temperature was slowly raised to 60° and the acetone was removed by distillation. The mixture was stirred at 60° for 2 hr. and at 85° for 1 hr. Dilution with water, extraction with chloroform, and evaporation of the latter gave a syrup which was dissolved in benzene (3 ml.). Slow addition of light petroleum and scratching induced crystallisation. The dimethyl ditrityl ether thus obtained (30 mg.) had m. p. 162—165°. Two recrystallisations raised the m. p. to 183° (from methyl*cyclo*hexane). Admixture with an authentic specimen (see below) caused no depression in m. p. The corresponding infrared spectra were superimposable.

The evaporated mother-liquor was chromatographed in light petroleum–benzene on alumina (Fisher; 10 g.), yielding upon elution with light petroleum–benzene (b. p. 40—60°) the trimethyl ditrityl ether (5 mg.) which was also identical in m. p., mixed m. p. and infrared spectrum with the corrresponding authentic specimen obtained by two alternative routes (see below).

Proof of Structure of Dimethyl Ditrityl Ether.—The following test was worked out. The compound (3 mg.) was dissolved in dioxan (5 drops) and concentrated nitric acid (*d* 1·42; 2 drops) was added. The mixture was kept at room temperature for 10 min. It was diluted with water (2 ml.), the precipitate of triphenylmethanol (when trityl derivatives were tested) was removed by filtration, and the filtrate was treated with sodium periodate solution [19] (1 drop). The dimethyl ditrityl ether gave a negative test and is therefore formulated as 2 : 4-di-*O*-methyl-1 : 5-di-*O*-tritylribitol.

Ribitol and 1 : 5-di-*O*-tritylribitol gave positive tests under these conditions. The trimethyl ditrityl ether (X) gave a negative test.

Ribitol by Reduction of Ribose with Sodium Borohydride.—Sodium borohydride (0·1 g.) in water (5 ml.) was added to a solution of D(−)-ribose (0·5 g.) in water (10 ml.). After being kept overnight at room temperature, the solution was acidified with acetic acid and evaporated to dryness. The residue was heated at 50—60° for 1 hr. with glacial acetic acid (5 ml.), acetic anhydride (5 ml.), and perchloric acid (0·2 ml.), then poured into ice-water and extracted with chloroform. The extract was dried (Na_2SO_4), and the solvent was removed at the water-pump, leaving a syrup (0·8 g.). The syrup was deacetylated by sodium methoxide (0·1 ml. of N-solution) in absolute methanol (12 ml.) at room temperature. Evaporation of the methanol gave a syrupy residue (0·4 g.) which slowly crystallised; it had m. p. 100—101° (from methanol) (lit.,[16] m. p. 102°).

Alternatively, the reduction mixture was acidified with acetic acid and evaporated to dryness. The residue was taken up in water (100 ml.) and the solution was passed through the

[16] Fischer, *Ber.*, 1893, **26**, 633.

acidic form of Amberlite IR-120 (5 g.). The effluent was then percolated through the hydroxylic form of Amberlite IRA-410 (5 g.). Evaporation gave a syrup which slowly crystallised, having m. p. 100—101°, identical with the product described above.

Tritylation of Ribitol.—Triphenylmethyl chloride (4·24 g.) was added to a solution of ribitol (1·12 g.) in dry pyridine (12 ml.). The mixture was kept at room temperature for 4 days. The precipitate was removed and working up was as described above for the natural product. The syrup obtained was triturated with benzene–methyl*cyclo*hexane, giving crystals (4·0 g.), m. p. 138—146°. These were dissolved in a small volume of chloroform and kept at room temperature for 24 hr. The *monotrityl derivative* deposited (0·6 mg.) had m. p. 134—135°, raised by two recrystallisation to 141·5° (from benzene; some sintering at 139°) (Found: C, 72·4; H, 6·6; O, 20·4. $C_{24}H_{26}O_5$ requires C, 73·1; H, 6·6; O, 20·3%).

The chloroform mother-liquor was evaporated to dryness and the residue was crystallised from a minimal volume of methanol. The *dityrityl derivative* thus obtained had m. p. 154—155° which was raised by further recrystallisation to 156° (from benzene–light petroleum or benzene–methyl*cyclo*hexane) (Found: C, 80·7; H, 6·5; O, 12·6. $C_{43}H_{40}O_5$ requires C, 81·1; H, 6·3; O, 12·6%).

The ditrityl derivative (100 mg.) was kept overnight with acetic anhydride (2 ml.) in pyridine (2·5 ml.) at room temperature, the solution was poured into ice-water, and the *triacetate* was removed by filtration; it had m. p. 161° (from methanol) (Found: C, 76·7; H, 5·9; O, 17·0. $C_{49}H_{46}O_8$ requires C, 77·1; H, 6·1; O, 16·8%).

Methylation of Ditritylribitol.—30% Sodium hydroxide solution (24 ml.) and dimethyl sulphate (9 ml.) in acetone (15 ml.) were alternately added with stirring at 50° to ditritylribitol (3·0 g.) in acetone (100 ml.). This procedure was repeated six times so that, in all, the volumes of the added reagents were 125 ml. of alkali and 63 ml. of dimethyl sulphate in 105 ml. of acetone. The mixture was worked up in the usual way (see above) and the syrup thus obtained (3·0 g.) was again methylated as described, yielding a crystalline precipitate, m. p. 164—166°, on trituration with benzene–methyl*cyclo*hexane (1·0 g.). Three recrystallisations gave the *dimethyl dityrityl ether*, m. p. 184° (from methyl*cyclo*hexane) (Found: C, 81·2; H, 6·9; O, 12·2; OMe, 9·1. $C_{45}H_{44}O_5$ requires C, 81·3; H, 6·7; O, 12·0; OMe, 9·3%). The mother-liquor was evaporated and the residue triturated with methyl*cyclo*hexane–light petroleum, affording a crystalline mixture (0·3 g.), m. p. 114—118°, of the above dimethyl ether, the trimethyl ether, and triphenylmethanol which was not separated into its components.

Separation was effected by dissolving the residue from evaporation of the mother-liquor in light petroleum and chromatography on alumina (50 g.; Fisher). Fractions of 25 ml. were taken. Elution with light petroleum gave methyl triphenylmethyl ether (200 mg.) which crystallised (m. p. 81°; from propan-1-ol–methanol) and then sublimed at 78°/0·03 mm. (Found: C, 87·6; H, 6·6; O, 5·8. Calc. for $C_{20}H_{18}O$: C, 87·6; H, 6·9; O, 5·6%).

Elution with light petroleum–benzene (60 : 40) gave the *trimethyl dityrityl ether* (0·5 g.), m. p. 155·5° (from propan-2-ol–methanol) (Found: C, 80·9; H, 6·9; O, 12·2; OMe, 13·5. $C_{46}H_{46}O_5$ requires C, 81·4; H, 6·8; O, 11·8; OMe, 13·7%). Further elution gave triphenylmethanol and partially methylated material which was not investigated.

Reduction of 2 : 3 : 4-Tri-O-methylribose and Tritylation of the Product.—2 : 3 : 4-Tri-*O*-methylribose [9] (220 mg.) was reduced in methanol (5 ml.) with sodium borohydride (50 mg.). After the usual working up the *diol* was obtained as a mobile liquid (200 mg.). No carbonyl absorption was exhibited in its infrared spectrum in chloroform.

To 2 : 3 : 4-tri-*O*-methylribitol (200 mg.), dissolved in dry pyridine, was added triphenylmethyl chloride (0·7 g.) and the mixture was kept at room temperature for 4 days. After the usual working up the residue (0·75 g.) was chromatographed on alumina (30 g.; Fisher). Elution with light petroleum–benzene (50 : 50) gave the trimethyl dityrityl ether as an oil which crystallised (m. p. 155—156°; from propan-2-ol–ethanol) and was identical with the product described above.

We thank Dr. A. B. Foster for ionophoretic mobility measurements on (−)-bornesitol, Dr. L. Anderson for authentic (±)-bornesitol and (±)-bornesitol penta-acetate, and the Planned Parenthood Federation of America, Inc., for a grant which made this work possible.

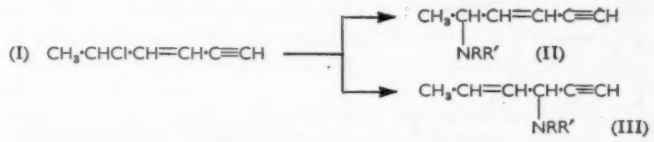
Department of Chemistry, Israel Institute of Technology,
Haifa, Israel. [*Received, April 9th,* 1958.]

648. *Researches on Acetylenic Compounds. Part LXII.* The Interaction of Amines and the Stereoisomers of 5-Chlorohex-3-en-1-yne.*

By Ian Bell, R. Madroñero, and M. C. Whiting.

trans-5-Chlorohex-3-en-1-yne reacts with a number of amines to give normal and abnormal (*i.e.*, non-conjugated) substitution products in proportions which vary widely from case to case and are much influenced by the solvent used and by the presence of small amounts of water. Earlier mechanistic suggestions are revised, and the results are correlated with differential solvent effects upon S_N1, S_N2, and S_N2' processes. The *cis*-chloride behaves differently, giving either pyrroles by cyclisation of the products of normal substitution, or unconjugated amines by abnormal substitution.

Reactions between 5-chlorohex-3-en-1-yne (I) and a number of amines were described by Jones, Lacey, and Smith.[1] While ammonia, aniline, and ethylamine behaved normally, giving the expected conjugated vinylacetylenic amines (II), diethylamine gave instead



3-diethylaminohex-4-en-1-yne (III; R = R′ = Et). Similar results were obtained with some related chlorides; they were explained on the assumptions that the products were in each case the most stable isomers, and that rearrangement was promoted by high basicity of the amine used and by the presence in the allylic chloride of substituents tending to increase the mobility of the anionotropic system.

These assumptions have seemed less plausible in recent years, and re-investigation of the reaction by Dr. J. B. Armitage in 1949 [2] revealed some discrepancies with the original experimental findings. The work of Young, Webb, and Goering,[3] amplified by Young, Clement, and Shih,[4] has provided the basis for a more acceptable rationalisation of the results of Jones *et al.*,[1] which have now been extended and generalised. Reactions between 5-chlorohex-3-en-1-yne—now known [5] to be a 3 : 1 mixture of stereoisomers—and amines were originally carried out in metal autoclaves; these experiments have given inconsistent results—usually lower yields—on attempted repetition, probably because corrosion introduced small amounts of metal halides which influenced the reaction. Working at lower temperatures with glass apparatus, we have examined the reactions of the pure *cis*- and *trans*-5-chlorohex-3-en-1-yne isomers with ethylamine and diethylamine, the amines mainly used by Jones *et al.*,[1] and also with several others. Higher yields were obtained; but the composition of the products was influenced by the presence of quite small quantities of water, so we controlled this factor also. It was possible at an early stage to identify products which were essentially homogeneous, and these were purified as crystalline salts and regenerated. With pure specimens of all the conjugated and two representative unconjugated amines available (see Table), quantitative analysi sof total reaction products by spectrophotometry became straightforward.

The case of *trans*-5-chlorohex-3-en-1-yne will be considered first. All amines, under

* Part LXI, *J.*, 1958, 1313.

[1] Jones, Lacey, and Smith, *J.*, 1946, 940.
[2] Armitage, unpublished work at Manchester.
[3] Young, Webb, and Goering, *J. Amer. Chem. Soc.*, 1951, **73**, 1076.
[4] Young, Clement, and Chih-Hua Shih, *ibid.*, 1955, **77**, 3061.
[5] Bell, Jones, and Whiting, *J.*, 1957, 2597.

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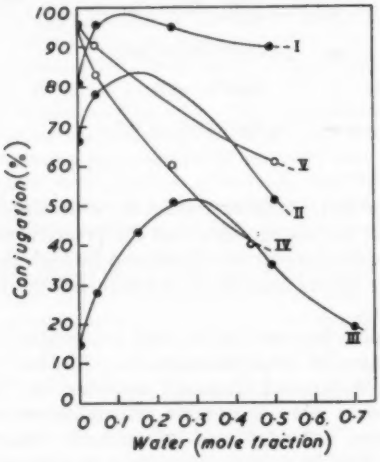
Amine	B. p./mm.	n_D	ε_{2230}	Amine	B. p./mm.	ε_{2230} *
(I; R = H, R′ = Et)	61·5°/20	1·4756 (18°)	13,400	(I; R = R′ = Me)	41°/15	13,600
(II; R = H, R′ = Et)	54°/20	1·4570 (20°)	170	(I; RR′ = $[CH_2]_5$)	94°/15	13,400
(I; R = R′ = Et)	75°/15	1·4738 (22°)	13,400	(I; R = H, R′ = Bu)	85°/15	13,400
(II; R = R′ = Et)	68°/22	1·4530 (21·5°)	560			

* Spectra were determined in EtOH; the conjugated, but not the unconjugated, amines showed maxima at 2230 ± 10 Å.

the conditions used, gave vinylacetylenic amines in total yields of up to 90%. The Figure shows the variation in the proportions of the two isomers formed when ethylamine, dimethylamine, *n*-butylamine, diethylamine, and piperidine were treated with the chloride in the presence of varying amounts of water. The two primary amines gave, under anhydrous conditions, almost pure conjugated amines, whereas addition of water resulted in the formation of mixtures, quite small quantities, especially when calculated on a weight or volume basis, having a marked effect. Qualitatively, it was clear that the addition of water was increasing the reaction rate. It is possible to explain these results simply by assuming that bimolecular substitution by primary amines proceeds without significant



Proportion of conjugated amine (II) *from* trans-5-*chlorohex*-3-*en*-1-*yne*.
● *Secondary amines* (I, Me_2NH; II, $[CH_2]_5NH$; III, Et_2NH).
○ *Primary amines* (IV, $Et{\cdot}NH_2$; V, $Bu{\cdot}NH_2$).

rearrangement [*i.e.*, $k(S_N2) \gg k(S_N2')$ in solvent amine], but that unimolecular substitution becomes more important as the reaction medium becomes more polar and gives a mixture in which the amount of unconjugated amine slightly outweighs that of its isomer. Acceleration of both reactions, but of S_N1 more than S_N2, would be predicted as the polarity of the medium is increased.[6] The unconjugated and conjugated isomers (I and II; R = H, R′ = Et) were both stable in the presence of ethylamine hydrochloride under the conditions used, and indeed under the more drastic conditions which were applied in unsuccessful attempts to effect anionotropic rearrangements.

The secondary amines behaved quite differently. Dimethylamine, piperidine, and diethylamine gave, in the absence of water, products containing respectively 81%, 66%, and 18% of the conjugated isomers. In each case, addition of water resulted in, first, an increase, to maxima of about 97%, 84%, and 50%, then a decrease to less than 90%, 50%, and 20%, respectively. The amounts of water required to give the maximal proportion of conjugated amine increased in the same order: dimethylamine, piperidine, diethylamine. Now, this order is not related to the basicity of the three amines used (dimethylamine < diethylamine ≪ piperidine); it is that of decreasing polarity, *considered as solvents*. We believe that in the anhydrous amines, reactions S_N2 and S_N2' proceed side by side; in

[6] Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 345 *et seq.*

dimethylamine, as in the primary amines studied, $k(S_N2) > k(S_N2')$, whereas in diethylamine the relation is inverted. This seems a reasonable assumption; the transition state for the S_N2 reaction shows considerable dipolar character, and its potential energy will be much affected by the ability of solvent molecules to stabilise the developing charges by dipole compensation and intermolecular hydrogen-bond formation. In S_N2' substitution, however, the attacking nucleophil almost certainly enters from the same side of the planar allylic system as that on which the chloride ion leaves;[3,7] the two centres of opposite charge are then close together, and the dipole moment is correspondingly smaller, while the formation of an intra-complex hydrogen bond[3] between the arriving and the departing group will, in this case, further reduce the need for solvation. Addition of water to the reaction mixture would be expected to stabilise the S_N2 transition state relative to that for S_N2' reaction, and so to increase the proportion of conjugated form; ultimately, however, it will accelerate unimolecular substitution to the point where this process becomes of greater importance, and the ratio of products will then approximate to that typical of the allylic carbonium ion, and varying to some extent, of course, with the amine.

When the *trans*-chloride was treated with "50%" aqueous acetonitrile under the conditions used for the reactions with amines it did in fact suffer hydrolysis; on distillation of the product, no chloride was recovered, but the hexenynol produced was heavily contaminated with higher-boiling compounds and showed strong bands in the C=O stretching region. Hydration of acetylenic compounds and addition of hydrogen chloride are possible under such conditions.

This interpretation is not, of course, rigorously proved; while the complete description of simple "carbonium ions" is still a matter of controversy, that of allylic and vinylacetylenic analogues is beyond the range of useful discussion. If, however, ion-pair or covalently solvated intermediates were postulated, their behaviour would presumably be similar as far as the present studies are concerned.

Except that products treated as individual isomers by the earlier workers are now seen to have contained about 4% (ethylamine) and 18% (diethylamine) of the unconjugated and conjugated amines, respectively, the above experimental results agree well with those earlier reported. The conversion of 5-ethylaminohex-3-en-1-yne into 3-diethylaminohex-4-en-1-yne on ethylation, which was described (30% yield) by Jones *et al.*[1] only in a footnote, would not be consistent with the present conclusions, since it would imply thermodynamic control of the reaction and an unexpected stability relation for the tertiary amines. This experiment was therefore repeated, both with neat reactants, as described[1] [but in glass apparatus (29% yield)], and in acetonitrile (58% yield). In each case the tertiary amine obtained consisted *entirely* (by spectrophotometry $\leqslant 96\%$) of the *conjugated* form. We can only assume that the actual specimen of the conjugated ethylamino-compound used in this experiment by the earlier workers had been prepared under non-anhydrous conditions and had contained enough of the unconjugated isomer to allow the isolation of 30% of its ethylated analogue after preferential destruction of the conjugated amine (which is in fact more easily resinified) under the vigorous conditions used.

The essence of the explanation just given for the striking difference between the behaviour of ethylamine and diethylamine is that as solvents they are of different polarity. If this is correct, it follows that in a medium of which the amine constitutes only a small part, the two amines will give much more similar products. This is apparently true for aqueous solutions (see Figure); although immiscibility prohibits the continuation of the curves, these do approach comparable values for the percentage of conjugated isomers in the two cases. Choice of alternative solvents is not easy, as when alcohols are used considerable quantities of alkoxyhexenynes result; acetone rapidly self-condenses in the reaction conditions used, while in light petroleum, benzene, or ether a second liquid phase, consisting of the amine and amine hydrochloride, separates. Acetonitrile proved satisfactory; in it ethylamine gave, in 82% yield, a product containing at least 99% of the

[7] Stork and White, *J. Amer. Chem. Soc.*, 1953, **75**, 4119.

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conjugated isomer, while diethylamine gave, in 46% yield, a product containing 84% of the conjugated isomer. A molar ratio 1 : 4 : 30 for chloride : amine : acetonitrile was used in each case. These reactions were also investigated kinetically at 35°; diethylamine gave good second-order rate constants up to 85% completion, providing that the equation used was that calculated for the reaction:

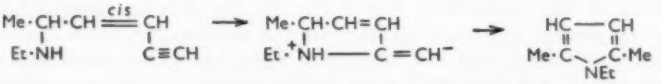
$$RCl + 2Et_2NH \longrightarrow R{\cdot}NEt_2 + Et_2NH.HCl \quad (\text{rate} = k[RCl][Et_2NH])$$

Evidently the acetylenic amines formed are much less basic than diethylamine (or ethylamine).[8] The rate constants in this case rose steadily during the reaction from $2{\cdot}26 \times 10^{-4}$ to $2{\cdot}48 \times 10^{-4}$ l. mole^{-1} min.$^{-1}$, presumably because of the expected primary salt effect. For ethylamine, the second-order rate constants fell rapidly, then rose slowly; the initial drop was greater when the initial chloride concentration was halved, and was almost certainly due to the presence, in the ethylamine used, of a trace of impurity (presumably ammonia or methylamine) which reacted more rapidly. The best estimates for the initial rate constants for ethylamine and diethylamine were $(4{\cdot}0 \pm 0{\cdot}2) \times 10^{-4}$ and $(2{\cdot}25 \pm 0{\cdot}05) \times 10^{-4}$ l. mole^{-1} min.$^{-1}$, respectively. If these results, obtained for 2M- and M-solutions, respectively, at 35°, are applicable relatively to the 2·5M-solutions at 50° used in the preparative experiments, it follows that the S_N2' reaction for diethylamine in acetonitrile is at least seven times faster than that for ethylamine in the same solvent, since 16%, as against <1%, of the unconjugated amine was formed. Evidently, then, the above explanation is not entirely adequate; diethylamine shows an intrinsic tendency to react by mechanism S_N2', for which the explanation is not obvious.

The use of acetonitrile in preparative work involving halide–amine reactions in allylic systems when normal replacement is required is clearly advantageous. Nitromethane, used as solvent in the reaction with ethylamine, gave, in 71% yield, a product containing only 83% of the conjugated isomer, and so is much less satisfactory.

In a system containing diethylamine, water, and acetonitrile (molar ratio about 1 : 8 : 3) a 71% yield of a product containing only 10% of the conjugated form was obtained; on the other hand ethylamine under similar conditions gave an essentially (78%) conjugated product. Though too complicated for mechanistic discussions, the former conditions may have preparative value for promoting abnormal substitution (see below).

Attention was next directed to the reactions of the *cis*-chloride. In acetonitrile, less than a 2% yield of basic material was obtained; the main product was 1-ethyl-2 : 5-dimethylpyrrole (62%). In anhydrous ethylamine the same product was obtained in smaller yield (18%), together with much recovered chloride (46%) and a little (~9%) 3-ethylaminohex-4-en-1-yne, under the same conditions as those in which the *trans*-chloride gave a 77% yield of amine. In aqueous acetonitrile (1 : 8 : 3) the main product (37% yield) was basic, and of this only 4% was the conjugated isomer. A little ethyldimethylpyrrole was present, with a larger quantity of *cis*-hex-3-en-5-yn-2-ol (total *ca.* 8%). Apparently use of acetonitrile again gives a clean, normal bimolecular substitution reaction, the product then undergoing cyclisation to the pyrrole. In excess of amine as solvent the S_N2

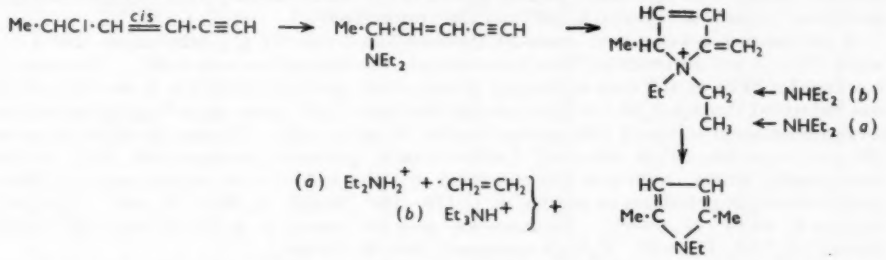


reaction is slower than that involving the *trans*-isomer, and the S_N2' process is able to compete fairly effectively. Under S_N1 conditions a carbonium ion is formed which for the most part reacts before equilibrating with its *trans*-isomer,[9] giving mainly the non-conjugated product.

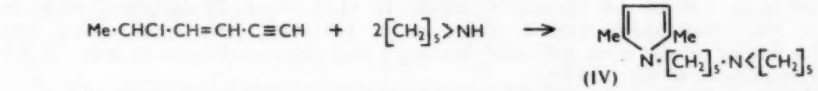
The reaction between the *cis*-chloride and diethylamine in acetonitrile took an unexpected course; the product was again 1-ethyl-2 : 5-dimethylpyrrole. Presumably

[8] Wolff and Ramin, *Annalen*, 1957, **610**, 67.
[9] Waters and de la Mare, *Ann. Reports*, 1953, **50**, 141.

the first formed *cis*-tertiary amine underwent cyclisation to a 1 : 1-dimethylpyrrolium ion (or its prototropic isomer), which lost an ethyl group by either (*a*) an elimination or (*b*) a substitution involving a second molecule of diethylamine:



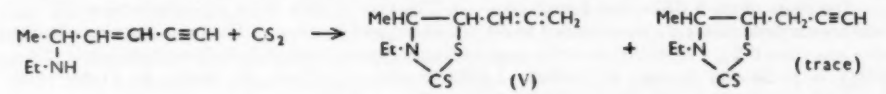
Rather than try to distinguish between these possibilities, we substituted piperidine for diethylamine, when (*a*) would lead to 2 : 5-dimethyl-1-pent-4′-enylpyrrole, and (*b*) to 1-(2 : 5-dimethyl-1-pyrryl)-5-piperidinopentane (IV). The product was clearly the latter, forming an unstable monohydrochloride and showing ultraviolet and infrared absorption spectra suggestive of a trisubstituted pyrrole.



In acetonitrile, diethylamine and the *cis*-chloride also gave a very small (2%) yield of basic material, largely (90%) unconjugated. This is less than the yield of unconjugated amine obtained from the *trans*-isomer (7%); evidently the S_N2' reaction with diethylamine is also inhibited by the *cis*-configuration. In contrast, the reaction in "50%" aqueous acetonitrile (1 : 8 : 3) gave almost as large a yield (66%) of basic product as did that of the *trans*-form, and it contained a mere 1·5% of the conjugated amine. This clear-cut result encourages the belief that in this case, at least, a genuine unimolecular reaction was being observed; the products bore no resemblance to those obtained in anhydrous acetonitrile, the pyrrole yield being below 1·5%.

The *cis*-chloride reacted rather sluggishly with aniline to give the known crystalline 2 : 5-dimethyl-1-phenylpyrrole.

Infrared spectra for the amines prepared were consistent with the structures proposed. 3-Ethylaminohex-4-en-1-yne was examined in carbon disulphide solution without complications due to reaction between the >NH and carbon disulphide groupings—presumably because of its relatively low basicity [8]—but when the conjugated isomer was similarly treated it gave a spectrum which included a strong band at 1951 cm.$^{-1}$. This band was



traced to the rapid formation of the allenic thiothiazolidone (V), which was isolated after distillation and separated by crystallisation from a small quantity of the acetylenic isomer formed concurrently.

Experimental

Preparation of Pure Amines.—*5-Ethylaminohex-3-en-1-yne.* *trans*-5-Chlorohex-3-en-1-yne [5] (90 g.), ethylamine (200 c.c.), and acetonitrile (1200 c.c.) were heated to 50° for 40 hr., under a water-condenser surmounted by a "cold-finger" condenser containing acetone and solid carbon dioxide (the latter was probably unnecessary, since there was no evidence of condensation in it). The ethylamine and about 900 c.c. of acetonitrile were distilled off, water was added, and the

basic fraction was isolated with ether. Distillation gave the amine (78·5 g., 81%), b. p. 61—62°/20 mm., n_D^{18} 1·4756, m. p. −5·5° to −4·5° (Jones *et al.*[1] report b. p. 72°/30 mm., $n_D^{13\cdot5}$ 1·4788). The α-naphthylurea formed needles, m. p. 126—127°, from aqueous ethanol, and the hydrochloride, prepared in dry ether, formed plates, m. p. 159·5—160·5°, from propan-2-ol–light petroleum (Jones *et al.*[1] give m. p. 127° and 158°, respectively).

3-Ethylaminohex-4-en-1-yne. trans-5-Chlorohex-3-en-1-yne (91 g.), ethylamine (200 c.c.), water (72 c.c.), and acetonitrile (72 c.c.) were mixed; the temperature rose to 60°. The mixture was kept for 24 hr. at 40°, then worked up, giving a basic product (72·5 g.), b. p. 66—75°, which was redistilled through a 50 × 1·8 cm. column filled with 1/16″ gauze rings [10] and fitted with a total-condensation still-head with manual control of reflux ratio. The first group of fractions (20 g.), b. p. 58—59°/18 mm., n_D^{19} 1·4594—1·4608, probably contained 90—95% of the unconjugated amine; a portion was converted into the *hydrochloride*, which separated from propan-2-ol–light petroleum as needles, m. p. 179—180° (Found: C, 60·4; H, 8·85. $C_8H_{14}NCl$ requires C, 60·15; H, 8·85%). Regeneration gave the *amine*, b. p. 54°/20 mm., n_D^{20} 1·4570 (Found: C, 77·7; H, 10·75. $C_8H_{13}N$ requires C, 78·0; H, 10·65%).

5-Diethylaminohex-3-en-1-yne. (*a*) 5-Ethylaminohex-3-en-1-yne (12·3 g.), ethyl bromide (21·8 g.), and acetonitrile (150 c.c.) were heated under reflux (internal temperature about 85°) for 24 hr. Isolation of the basic fraction with ether and distillation gave a liquid (11·25 g.), which was treated with light petroleum and phenyl *iso*cyanate (10 g.). The phenylurea was separated by filtration, and the basic fraction again isolated and distilled, giving *5-diethylaminohex-3-en-1-yne* (8·8 g.), b. p. 74—76°/15 mm., $n_D^{21\cdot5}$ 1·4736—1·4740; after redistillation it had n_D^{22} 1·4738, m. p. −6° to −4° (Found: C, 79·15; H, 11·15. $C_{10}H_{17}N$ requires C, 79·4; H, 11·35%). The hydrochloride formed prisms, m. p. 147—148°, from ethyl acetate; the *methiodide* formed prisms, m. p. 183—184° (decomp.), from acetone (Found: C, 44·9; H, 6·7. $C_{11}H_{20}NI$ requires C, 45·05; H, 6·9%).

(*b*) The secondary amine (12·3 g.) and ethyl bromide (43·6 g.) were heated under reflux (internal temperature 53°) for 24 hr. The tertiary amine formed was isolated as above (4·35 g.), having b. p. 88—90°/27 mm., n_D^{20} 1·4704—1·4708, with an extinction coefficient at 2230 Å almost equal to that of the above specimen.

3-Diethylaminohex-4-en-1-yne. 3-Ethylaminohex-4-en-1-yne (2·25 g.), ethyl bromide (10 g.), and acetonitrile (75 c.c.) were heated under reflux for 24 hr. (internal temperature 75°). Isolation of the tertiary amine as above gave *3-diethylaminohex-4-en-1-yne* (1·35 g.), b. p. 68°/22 mm., $n_D^{21\cdot5}$ 1·4530—1·4532 (Found: C, 79·3; H, 11·2%). The hydrochloride formed prisms, m. p. 146—147°, from benzene (Jones *et al.*[1] report b. p. 68°/19 mm., $n_D^{19\cdot5}$ 1·4552 for the amine and m. p. 144° for the hydrochloride).

The other conjugated amines (I = NMe_2, NHBu, $N[CH_2]_5$) were isolated from the products of analytical experiments as described below.

Analytical Experiments.—Ethylamine and dimethylamine were stored over potassium hydroxide and dried with sodium and lithium; there was some evidence that the deep blue colour of the metal solution was obtained most quickly when both metals were used. They were distilled directly into the cooled reaction vessel. Diethylamine was fractionated under partial reflux. *n*-Butylamine and piperidine were distilled over sodium. Results are tabulated and, in part, discussed further below.

Reactions of cis-*5-Chlorohex-3-en-1-yne.*—(*a*) The *cis*-chloride (11·4 g.), ethylamine (26 c.c.), and acetonitrile (200 c.c.) were heated to 50° for 48 hr. under reflux. The basic fraction obtained was less than 0·2 g.; distillation of the neutral fraction gave 1-ethyl-2 : 5-dimethylpyrrole (7·6 g., 62%), b. p. 56—58°/9 mm., n_D^{21} 1·4904—1·4908 (Found: C, 77·85; H, 10·75; N, 11·25. Calc. for $C_8H_{13}N$: C, 78·0; H, 10·65; N, 11·35%). The pyrrole showed no absorption maximum above 2000 Å, but at that wavelength had ε 9000 (Hazelwood *et al.*[11] give b. p. 102°/79 mm.).

(*b*) Experiments 1, 5, 7, 8, and 15 were repeated with the *cis*-chloride, and are numbered with asterisks:

Expt. 1* gave unchanged chlorohexenyne (2·6 g., 46%), ethyldimethylpyrrole (1·12 g., 18%), and an amine fraction (0·5 g., 9%), mainly unconjugated but difficult to free from a little pyrrole.

Expt. 5* gave a basic fraction (2·27 g., 37%) which contained only 4% of the conjugated isomer (derived from 1—2% of *trans*-chloride as impurity?). The neutral fraction (0·41 g.),

[10] Dixon, *J. Soc. Chem. Ind.*, 1949, **68**, 88, 119.
[11] Hazlewood, Hughes, and Lions, *Proc. Roy. Soc. New South Wales*, 1937, **71**, 92.

Analytical experiments with trans-5-*chlorohex*-3-*en*-1-*yne*.

Expt.	Amine	(c.c.)	Water (c.c.)	MeCN (c.c.)	Temp.	Time (hr.)	Yield (%)	Conjugn.* (%)	Remarks
1	$EtNH_2$	13	6	0	20°	96	77	95	*a*
2	,,	75	1·1	0	20	96	82	83	*a*
3	,,	75	7·1	0	20	96	81	60	*a*
4	,,	75	21·5	0	20	96	76	40	*a*
5	,,	13	37·5	37·5	50	24	36	93	*b*
6	,,	50	7·1	20·5	20	96	83	78	*a*
7	Et_2NH	21	0	0	65	24	59	14	*c*
8	,,	42	0	150	50	24	46	84	*d*
9	,,	75	0·6	0	60	24	51	28	
10	,,	75	2·5	0	60	24	63	43	*a*
11	,,	75	4·4	0	60	24	73	51	*a*
12	,,	75	13·1	0	60	24	76	35	*a*
13	,,	50·4	22·1	0	60	24	71	19	*e*
14	,,	75	4·4	12·7	60	24	76	53	*a*
15	,,	21	37·5	37·5	50	24	71	10	*a*
16	Me_2NH	15	0	0	20	96	81	81	*a*
17	,,	75	1·0	0	20	96	73	96	*a*
18	,,	75	6·5	0	20	96	76	95	*a*
19	,,	75	19·6	0	20	96	76	90	
20	$BuNH_2$	21	0	0	65	24	55	96	
21	,,	75	0·65	0	65	24	74	91	
22	,,	75	13·8	0	65	24	16	61	
23	$(CH_2)_5NH$	30	0	0	65	24	63	66	
24	,,	75	0·5	0	65	24	61	78	
25	,,	75	4·6	0	65	24	61	83	
26	,,	75	14·5	0	65	24	63	52	

* The percentages of conjugated isomer were obtained spectrophotometrically, by using the listed $\varepsilon_{max.}$ values for the conjugated amines and the ε_{2230} values (no maximum) of the ethylamino- and diethylamino-compounds (III) for secondary and tertiary unconjugated amines, respectively. Results are, of course, quite insensitive to small variations in the latter.

(*a*) Neutral fraction $>$100 mg., not investigated; (*b*) neutral fraction yielded 1·7 g. (35%) of an alcohol, b. p. 92°/60 mm., n_D^{20} 1·4846, $\lambda_{max.}$ 2230 Å, ε 13,000, evidently essentially (~93%) *trans*-hex-3-en-5-yn-2-ol; (*c*) neutral fraction yielded 0·31 g. (5·5%) of unchanged chloride; (*d*) in expt. 8, 11·4 g. of the chlorohexenyne were used; (*e*) in expt. 13, 3·84 g. of the chlorohexenyne were used.

b. p. 65—69°/18 mm., n_D^{19} 1·4762—1·4798, was shown by its infrared spectrum to be a mixture of *cis*-hex-3-en-4-yn-2-ol and some ethyldimethylpyrrole. 2 : 5-Dimethylfuran was sought but not found.

Expt. 7* was continued for 72 hr. instead of 24 hr. The basic fraction (2·5 g., 33%) contained 9% of the conjugated form. The neutral fraction (0·23 g.), b. p. 100—120° (bath temp.)/76 mm., n_D^{22} 1·4802, was a mixture of ethyldimethylpyrrole and unchanged chloride.

Expt. 8* gave a basic fraction (0·33 g., 2%), containing 12% of the conjugated tertiary amine, the remainder being 3-diethylaminohex-4-en-1-yne. The neutral fraction yielded 1-ethyl-2 : 5-dimethylpyrrole (3·6 g., 29%), b. p. 58°/13 mm., n_D^{22} 1·4880—1·4892, with ultraviolet and infrared spectra identical with those of the specimen obtained from ethylamine.

Expt. 15* was carried out at 65° instead of 50°. The basic fraction (5·0 g., 66%) contained only 1·5% of the conjugated amine; it had b. p. 66—68°/16 mm., $n_D^{21\cdot5}$ 1·4522—1·4524, and showed the same infrared spectrum as did the amine obtained by ethylation of the secondary amine. The neutral fraction contained less than 100 mg.

(*c*) 1-(2 : 5-Dimethyl-1-pyrryl)-5-piperidinopentane (IV). *cis*-2-Chlorohex-3-en-5-yne (11·4 g.), piperidine (40 c.c.), and acetonitrile (150 c.c.) were heated to 50° for 48 hr. Distillation of the basic fraction gave a fore-run (2·55 g.; b. p. *ca.* 50°/0·05 mm., n_D^{21} 1·4890—1·4896), apparently mainly 3-piperidinohex-4-en-1-yne, then the expected *pentane* (4·7 g., 19%), b. p. 110—112°/0·05 mm., n_D^{21} 1·5070 (after redistillation) (Found: C, 77·25; H, 11·15; N, 11·1. $C_{16}H_{28}N_2$ requires C, 77·35; H, 11·35; N, 11·3%), $\lambda_{max.}$ 2160 Å (ε 6800 in EtOH). The *hydrochloride* formed unstable prisms, m. p. 179—180°, from benzene (Found: C, 66·95; H, 9·95. $C_{16}H_{29}N_2Cl$ requires C, 67·45; H, 10·3%).

(*d*) 2 : 5-Dimethyl-1-phenylpyrrole. The *cis*-chloride (5·73 g.), aniline (18·5 c.c.), and acetonitrile (75 c.c.) were heated to 55° for 75 hr. Distillation of the neutral fraction gave a liquid (0·83 g., 10%), b. p. 60—61°/0·05 mm., n_D^{19} 1·5650—1·5658, which yielded prisms, m. p. 50·5—51·5° (from pentane at −30°) (Hazlewood *et al.*[11] give m. p. 51—52°).

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Isolation of Pure Products from Analytical Experiments.—*5-Dimethylaminohex-3-en-1-yne.* The product from expt. 17 was dissolved in dry ether, and a solution of hydrogen chloride in ether was added slowly. The precipitate crystallised from *iso*propyl alcohol–light petroleum, giving hygroscopic plates (1·6 g.), m. p. 122—123°, of the *hydrochloride* (Found: C, 60·9; H, 9·0; N, 8·3; Cl, 21·7. $C_8H_{14}NCl$ requires C, 60·2; H, 8·75; N, 8·75; Cl, 22·2%). The *amine*, obtained by regeneration, had b. p. 45°/15 mm. (Found: C, 78·05; H, 10·8; N, 11·1. $C_8H_{13}N$ requires C, 78·05; H, 10·55; N, 11·4%).

5-n-Butylaminohex-3-en-1-yne. The product from expt. 20 gave the *hydrochloride* as needles, m. p. 137—138°, from ethyl acetate (Found: C, 64·4; H, 9·6; N, 7·45; Cl, 18·5. $C_{10}H_{18}NCl$ requires C, 64·0; H, 9·6; N, 7·45; Cl, 18·9%). After regeneration the *amine* had b. p. 85—86°/15 mm. (Found: C, 78·6; H, 11·0; N, 9·45. $C_{10}H_{17}N$ requires C, 79·4; H, 11·3; N, 9·25%).

5-Piperidinohex-3-en-1-yne. The products from expts. 24 and 25 were combined and fractionated; although the b. p. did not vary sensibly from 31°/0·02 mm., the $E_{1\,cm.}^{1\%}$ values varied from 470 to 800. Those with $E_{1\,cm.}^{1\%}$ >670 were combined and converted into the *hydrochloride*, which after crystallisation from ethanol had m. p. 178—179° (Found: C, 65·9; H, 9·1; N, 7·15; Cl, 18·0. $C_{11}H_{18}NCl$ requires C, 66·1; H, 9·05; N, 7·05; Cl, 17·8%). After regeneration, the *amine* had b. p. 94°/15 mm. (Found: C, 80·7; H, 10·35; N, 9·0. $C_{11}H_{17}N$ requires C, 81·0; H, 10·35; N, 8·6%).

1-Ethyl-4-propadienylthiazolin-2-thione. To a solution of carbon disulphide (25 c.c.) in dry ether (50 c.c.), 5-ethylaminohex-3-en-1-yne (10 g.) was added dropwise with cooling to 10°. After 24 hr. at 20° the ether was evaporated and the product was distilled at 120° (bath temp.)/10^{-4} mm., a good yield of a liquid, n_D^{21} 1·6190, being obtained; it solidified and had m. p. *ca.* 31°, raised after four crystallisations from ether to 50—51° (Found: C, 54·35; H, 6·5. $C_9H_{13}NS_2$ requires C, 54·25; H, 6·6%). (The distilled product showed weak absorption at 3300 cm.$^{-1}$, evidently due to a trace of the prop-2′-ynyl analogue and removed by recrystallisation.) A light-absorption maximum was at 2770 Å (ε 16,000).

Kinetic Measurements.—Procedure. The chloride (5·73 g.) was weighed into a 100 c.c. volumetric flask, and pure acetonitrile (30 c.c.) was added, followed by a cold solution of the dried amine in acetonitrile; the mixture was made up to 100 c.c. and at once immersed in the thermostatic bath. Zero time was taken as 4 min. after addition of amine, or 3 min. after immersion in the bath. Aliquot parts (approx. 5 c.c.) were run into ether (25 c.c.) and shaken with water (25 c.c.). The aqueous layer was twice more extracted with ether (25 c.c.), and 7M-nitric acid was added to neutrality (phenolphthalein), followed by an additional 3 c.c. An excess of standard silver nitrate solution, followed by nitrobenzene (2 c.c., A.R.) and 40% ferric ammonium sulphate solution (1 c.c., containing a little nitric acid), was added, and the solution was titrated with potassium thiocyanate solution.

The rate constant k (see Table) was calculated from the equation:

$$k = \frac{2{\cdot}303}{t(2a - b)} \log \frac{b(a - x)}{a(b - 2x)}$$

where a and b were the original molar concentrations of chlorohexenyne and amine, and x was the chloride-ion concentration after t minutes.

(i) *Ethylamine*; b = 2·035M; 35·1° ± 0·1°.

a = 0·500M			a = 0·250M		
t (min.)	x (M)	10^4k (min.$^{-1}$)	t (min.)	x (M)	10^4k (min.$^{-1}$)
120	0·0581	5·23	120	0·0307	5·48
240	0·0892	4·24	230	0·0481	4·70
470	0·1514	4·10	475	0·0863	4·60
1440	0·3173	4·25	1205	0·1548	4·33
1830	0·3588	4·38	1887	0·1942	4·45
3000	0·4252	4·37	2650	0·2174	4·42
4335	0·4645	4·53	3300	0·2290	4·39

(ii) *Diethylamine*; a = 0·1016M; b = 0·9565M; 35·1° ± 0·1°.

t (min.)	x (M)	10^4k (min.$^{-1}$)
480	0·0098	2·26
1320	0·0249	2·29
1925	0·0340	2·30
2780	0·0455	2·36
3360	0·0518	2·36
4200	0·0596	2·37
4840	0·0650	2·40
6120	0·0732	2·41
7740	0·0818	2·48

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THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, April 16th*, 1958.]

649. *The Transmission of Electronic Effects through a Palladium Atom.*

By J. Chatt, L. A. Duncanson, and L. M. Venanzi.

The N–H stretching frequencies and band intensities of a series of palladous complexes *trans*-[L,amPtCl$_2$] [L = PR$_3$, P(OR)$_3$, AsR$_3$, R$_2$S, R$_2$Se, R$_2$Te, piperidine, and *n*-octylamine; " am " = piperidine, *n*-octylamine, and *p*-toluidine] have been measured. The effects transmitted from the ligand L across the palladium atom to the N–H bond are mainly electrostatic. There appears to be direct interaction between the *N*-hydrogen atom and filled *d*-orbitals of the metal. The frequency–intensity relationship and the half-band widths of the piperidine complexes are discussed.

The N–H stretching frequencies of a series of complexes of the general type *trans*-[L,amPtCl$_2$] (" am " = primary or secondary amine) show that differences between the electronic effects transmitted through the platinum atom from ligands L such as MR$_3$ (M = N, P, As, Sb) and R$_2$Q (Q = S, Se, Te) to the amine are mainly inductive.[1] Nevertheless, anomalies, which are just significant in the phosphine (L = PR$_3$) and marked in the ethylene complexes (L = C$_2$H$_4$), indicate that there is a second mode of transmission. This second mode is probably mesomeric, owing to the interaction of the filled orbitals of d_{xy}-type (or dp-hybrid) of the metal atom with vacant low-energy orbitals of suitable symmetry in the ligands L, and with the *N*-hydrogen atoms of the amine.

We now describe a similar study of an analogous series of palladium complexes. Since, in general, palladium(II) is not so easily oxidised to palladium(IV) as platinum(II) to platinum(IV), it seems that the electrons in the *d*-orbitals of palladium lie at a rather lower energy level and would not be so readily available for double bonding and so transmitting

Table 1. N–H *Stretching frequencies* ν (*cm.*$^{-1}$), *band intensities* B (*cm.*$^{-2}$ *molecules sec.*$^{-1}$), *and apparent half-band widths* $\Delta\nu_{\frac{1}{2}}^{a}$ (*cm.*$^{-1}$), *of the compounds* trans-[L,pipPdCl$_2$] *in carbon tetrachloride solution.*

L	ν	10^7B	$\Delta\nu_{\frac{1}{2}}^{a}$
Piperidine ...	3237	3·14 *	19·8
Et$_2$S	3238	—	—
Et$_2$Se	3240	—	—
Et$_2$Te	3249	—	—
AsEt$_3$	3252	1·12	17·5
PEt$_3$	3254	1·13	17·0
PPr$^n_3$	3254	1·14	17·5
PPh$_3$	3247	1·49	20·1
P(OMe)$_3$ ...	3250	1·27	17·2
P(OPh)$_3$ ...	3247	1·30	17·3

* This figure must be halved for comparison with the others since the complex contains two independent but identical N–H groups.

Table 2. N–H *Stretching frequencies* ν (cm.$^{-1}$) *of the monomeric complexes* trans-[L,amPdCl$_2$] *in carbon tetrachloride solution.*

L	am = *n*-Octylamine		am = *p*-Toluidine	
n-Octylamine...	3335	3271	—	—
Pr$^n_2$S	3339	3274	3348	3281
Pr$^n_2$Se	3340	3276	3350	3281
Pr$^n_2$Te	3345	3280	3359	3286
AsPr$^n_3$	3348	3283	3362	3289
PPr$^n_3$	3351	3285	3365	3291
P(OMe)$_3$	3348	3280	3362	3286
PPh$_3$	3348	3279	3360	3285
P(OPh)$_3$	3345	3280	3358	3286

mesomeric effects. Thus anomalies due to mesomeric effects should be smaller in the palladium series of complexes. Unfortunately, the ligand ethylene (L = C$_2$H$_4$) which gave the largest anomalies in the platinum series would not form a palladium compound, *trans*-[C$_2$H$_4$,amPdCl$_2$], suitable for similar investigations. Nevertheless, the slight anomalies of the triethylphosphine complexes are smaller in the palladium series.

The compounds examined, together with the relevant spectroscopic data, are listed in Tables 1 and 2. It was not possible to measure the band intensities or half-band widths

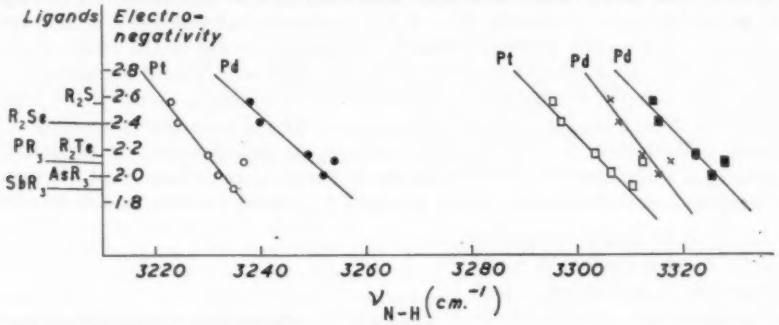
[1] Chatt, Duncanson, and Venanzi, *J.*, 1955, 4461.

XUM

of the piperidine complexes with L = Et_2S, Et_2Se, or Et_2Te, because the complexes were too unstable to be isolated. The *n*-octylamine series of complexes analogous to the *p*-toluidine complexes was examined to provide a complete series of secondary amine complexes, including a diamino-complex soluble in carbon tetrachloride. In the platinous complexes this requirement was met by the compound *trans*-[pepy,tolPtCl_2] (pepy = *n*-pentylpyridine; tol = *p*-toluidine). We could not prepare the palladous analogue or other mixed amine complexes in the palladous series, and resorted to *n*-octylamine complexes because the alternative, *trans*-[tol_2PdCl_2], is insoluble in carbon tetrachloride. Amino-palladous complexes containing trialkylstibines or ethylene were too unstable to be obtained, even in solution.

Useful information about electronic interactions in the complexes is obtained first from a consideration of frequencies alone and then from the relation between the frequencies and square-roots of the intensities of the N–H stretching bands of the piperidine complexes: the square-roots of the intensities were plotted as being the more fundamental property since they are proportional to the rate of change of the dipole moment of the bond during

FIG. 1. *Relation between the electronegativity of the ligand atom in* L *and the* N–H *stretching frequencies* ν_{N-H} *of the complexes* trans-[L,amMCl_2] *in carbon tetrachloride at* 20° (M = Pt or Pd).



Round symbols: Piperidine complexes.
Square symbols: *p*-Toluidine complexes. The mean of N–H stretching frequencies is plotted.
Crosses: *n*-Octylamine complexes.
Electronegativities are Pritchard and Skinner's " best values " (*Chem. Rev.*, 1955, **55**, 767).

the vibration. Over the short range of intensities and frequencies available the plot of frequency against intensity is also linear. Our conclusions are as follows:

(1) The influence of the ligands L on the N–H stretching frequencies (ν_{N-H}) is largely electrostatic. The plot of the frequencies against the electronegativities of the donor atoms in the closely similar alkyls gives a good straight line (Fig. 1), but the phosphines are anomalous, as in the platinous series.* However, as was expected, the phosphine points lie nearer to the lines in the case of palladium than of platinum, supporting the view that the anomalies are due to a mesomeric interaction. Nevertheless, the correspondence between the palladium and platinum plots is very close.

(2) The frequencies ν_{N-H} in the palladous series of complexes are generally 15—20

* A. L. Allred and F. Basolo have suggested personally that the anomalous position of the phosphines may be due to an error in the value assigned to the electronegativity of phosphorus. This had occurred to us and been rejected because no single value of the electronegativity of phosphorus would remove the anomaly from both plots. To bring the phosphine point to the palladium line would require phosphorus to have an electronegativity of 1·95, between that of arsenic (2·0) and antimony (1·9), in accordance with the suggestion of Allred and Rochow (*J. Inorg. Nuclear Chem.*, 1958, **5**, 264; 269). This is a possibility. If this value for the electronegativity of phosphorus were adopted, some anomaly would still remain in the case of platinum, and this we consider to be due to double bonding to phosphorus. To bring the phosphine point to the platinum line, phosphorus would have to be assigned an electronegativity of 1·8, even lower than that of antimony.

cm.$^{-1}$ higher than in their platinous analogues. This is consistent with the commonly-accepted view that palladium(II) is a poorer acceptor of electrons from its ligands than is platinum(II), so causing the nitrogen atoms to be more negatively charged than in the platinum analogues and ν_{N-H} to be higher.[1]

These differences in frequency cannot be due to the difference between atomic masses of the two metals. We can consider the hypothetical non-linear triatomic molecules Pt–N–H and Pd–N–H to obtain an approximate measure of the effect of changing the mass of the metal atom upon the N–H stretching frequencies. If a valence-force field [2] is assumed there is no mass effect of the metal atom upon the N–H frequency. Even if we go to the other extreme and assume a force-field which would allow the mass of the metal atom to play a large part in determining the N–H stretching frequency (*i.e.*, by postulating a strong Pt–H or Pd–H bond and a weak N–H bond), the change in mass of the metal from 195 to 107 atomic mass units cannot raise the stretching frequency of the bond to the hydrogen atom by more than about 5—6 cm.$^{-1}$. This being an extreme case it is safe to

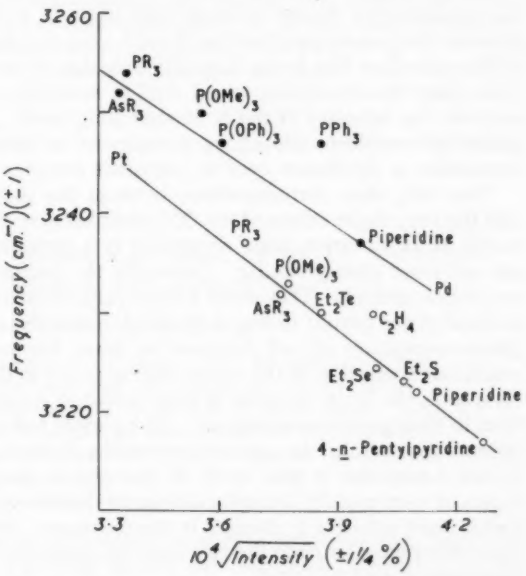


FIG. 2. N–H *Stretching frequencies and band intensities of complexes* trans-[L,pipPtCl$_2$] *and* trans-[L,pipPdCl$_2$].

assume that the principal causes of the lower frequencies of the N–H stretching bands of an amine in its platinous as compared with its analogous palladous complexes are electronic in origin.

(3) In the piperidine complexes *trans*-[L,pipPtCl$_2$] we found a linear relation between the frequencies and square roots of the intensities of the N–H bands, except for the phosphine and ethylene complexes.[1] Unfortunately, data relating to the palladous analogues are not nearly so complete. However, if we plot the relation and draw a line through the points relating to palladous complexes in a position corresponding to the best line through the platinous points we probably have comparable graphs for both series of complexes (Fig. 2).

It is noteworthy that these two graphs do not coincide so that one becomes an extension of the other, but instead the palladium graph is displaced to the side of higher intensity relative to the platinum graph. To explain why the point relating to *trans*-[C_2H_4,pipPtCl$_2$] lies significantly to the side of the higher intensity, we suggested that in all the platinous

[2] Lechner, *Monatsh.*, 1932, **61**, 385.

piperidine complexes the proton or N–H bond interacts with the electrons in the d_{xy}-type of orbitals on the platinum atom.[1] This was necessary because the frequency and intensity of N–H vibration vary independently, and we need two routes from the ligand L across the platinum atom to the hydrogen atom to allow this. The first and obvious route is inductive through the nitrogen atom. The second can only be mesomeric, directly through a d_{xy}-type of orbital of the metal interacting with suitable orbitals in the ligand L and the N–H bond. This interaction might be a type of hyperconjugation if the electron drift is from the N–H bond towards the platinum atom, which has a vacant p_z orbital to receive electrons, or an intramolecular hydrogen bond if the drift is from the *d*-orbitals of the metal to the proton. We consider the latter more likely in the case of platinum since its *d*-orbitals are all filled and it tends to form dative π-bonds better than most metals in their normal valency states. This intramolecular hydrogen bond can also be looked upon as orbital-following of the N–H stretching vibration, or screening of the proton by electrons in a non-bonding *d*-orbital of the metal.

All chemical evidence points to the electrons in the *d*-orbitals of palladium(II) being less available for double bonding than those in platinum(II), and so weaker interaction between the proton and electrons should occur in palladous complexes. The displacement of the palladium line to the high-intensity side of the platinum line is consistent with this view, since the interaction would tend to neutralise dipole changes in the N–H bond and so lower the intensity of the N–H stretching band. The scatter of the points relating to palladous complexes containing phosphorus as ligand atoms (Fig. 2) suggests that the interaction is significant even in palladous complexes.

The very close correspondence between the platinum and palladium plots in Fig. 1 and the very slight effects of the difference between the atomic weights of the metal atoms on the N–H vibration being considered it is perhaps surprising that the graphs in Fig. 2 are not more closely similar. Generally the points relating to the palladous complexes are more scattered. They cover a wider range of frequency corresponding to the differences in slope of the graphs in Fig. 1 (piperidine complexes). Also the points relating to phosphorus complexes are all displaced to lower frequencies and to higher intensities than would be expected from the corresponding points in the platinum graph. In the palladous complexes the N–H vibration is more sensitive to the electronic effects of the ligands, L, than in their platinous analogues. The greater number of electrons in the platinum atom appears to neutralise to a greater extent the electronic effects during transmission through it, and it may also be that the N–H vibration in the palladous complexes takes place in a region of more rapidly changing *d*-electron density so that the intensity of infrared absorption is more sensitive to changes in the mesomeric effect of L. Whatever the cause of the slight differences between the two series of complexes the exceptional position of triphenylphosphine should be noted.

The apparent half-band widths of the N–H stretching bands in the spectra of the piperidine complexes *trans*-[L,pipPdCl_2] have been recorded. They fall mainly in the range 16—18 cm.$^{-1}$ in both the palladous and platinous [1] series, but there are two notable exceptions. The narrowest band occurs in *trans*-[C_2H_4,pipPtCl_2] (13·8 cm.$^{-1}$), where we expect the direct Pt–H interaction to be least amongst the platinous complexes, and the widest occurs in *trans*-[pip_2PtCl_2] (22·6 cm.$^{-1}$).

There are probably many factors which affect band width in these molecules and they are not fully understood but it seems possible that the large width of the band in *trans*-[pip_2PtCl_2] is at least partly due to coupling of the two N–H bonds. This coupling is unlikely to be mechanical because of the large mass of the platinum atom and also because it appears to be less in the corresponding palladium complex. However, the difference in band width between the dipiperidine complexes of $PtCl_2$ and $PdCl_2$ is consistent with the orbital-following hypothesis of the interaction between the N–H bonds and the non-bonding *d*-orbitals of the metal atoms. Thus in these complexes the two N–H bonds can couple electronically through a *d*-orbital of the metal and such coupling

should be weaker in palladium than in platinum complexes. This explanation of variations in the band widths must, however, be treated with some reserve as the complex *trans*-[PPh_3,piperidine$PdCl_2$] has an exceptionally large half-band width of the same magnitude as that of *trans*-[pip_2PdCl_2] and this explanation could not apply here.

Experimental

Microanalyses are by Messrs. W. Brown and A. G. Olney of these laboratories.

The compounds *trans*-[L,am$PdCl_2$] were obtained by the reaction of the amine, am, with the bridged compound, $L_2Pd_2Cl_4$.[3] The mixed complexes containing R_2S, R_2Se, and R_2Te could not be isolated, but their spectra were obtained by dissolving the appropriate solid bridged compound together with its equivalent of amine in carbon tetrachloride and examining the spectrum of the solution. All the measurements where am is *n*-$C_8H_{17}\cdot NH_2$ were carried out by this method, and the pure complexes were not isolated.

trans-*Bis*-n-*octylaminedichloropalladium*.—Ammonium dichloropalladite (1 g.) and *n*-octylamine (2 c.c.) were warmed until a white solid formed. The mixture was cooled, and concentrated hydrochloric acid added. The yellow-orange solid formed was filtered off, dried, and recrystallised twice from ethanol and once from ether, m. p. 113—114° (Found: C, 44·0; H, 8·6; N, 6·6. $C_{16}H_{38}N_2Cl_2Pd$ requires C, 44·1; H, 8·8; N, 6·4%).

The spectra were measured at 25° ± 1° exactly as described in ref. 1.

Imperial Chemical Industries Limited,
Akers Research Laboratories,
The Frythe, Welwyn, Herts.

[*Received, April 9th*, 1958.]

[3] Chatt and Venanzi, *J.*, 1957, 2445.

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650. *Vapour Pressures of Metal Alkoxides. Part I. Titanium Tetra-*tert.*-butoxide and -amyloxide.*

By D. C. Bradley and J. D. Swanwick.

Vapour-pressure measurements in the range 0·05—50 mm. have been made on titanium tetra-*tert.*-butoxide and -amyloxide, by a static method, in an all-glass apparatus incorporating a novel type of spoon-gauge. The apparatus and technique were developed for compounds which are sensitive to hydrolysis and to thermal decomposition. The computed results conformed to equations of the type, $\log P = C - x/T - y \log T$ for certain ranges, but it is believed that their extrapolation is valid.

Recent work in these laboratories on the preparation of volatile metal alkoxides suggested the possibility of separating and purifying metals by fractional distillation of the alkoxides. It was necessary therefore to determine vapour pressures accurately over a wide range of pressures. In addition these data were required for calculations of thermodynamic properties and thermochemical data. Preliminary measurements of the boiling points of monomeric alkoxides of titanium,[1] zirconium,[1] and hafnium [2] at various pressures had revealed that their volatilities were in the unexpected order, $Hf(OR)_4 > Zr(OR)_4 > Ti(OR)_4$, whose theoretical implications [3] provided yet another need for vapour-pressure measurements of the highest possible accuracy. Considerable difficulties were experienced in attempting these accurate measurements and the present communication is mainly devoted to describing the experimental method. The titanium alkoxides were studied first because experience has shown that they are less difficult to deal with than the zirconium and the hafnium compounds. The results obtained were of sufficient accuracy to require a "three-constant" vapour-pressure equation.

[1] Bradley, Mehrotra, and Wardlaw, *J.*, 1952, 4204.
[2] *Idem*, *J.*, 1953, 1634.
[3] Bradley, *Nature*, 1954, **174**, 323.

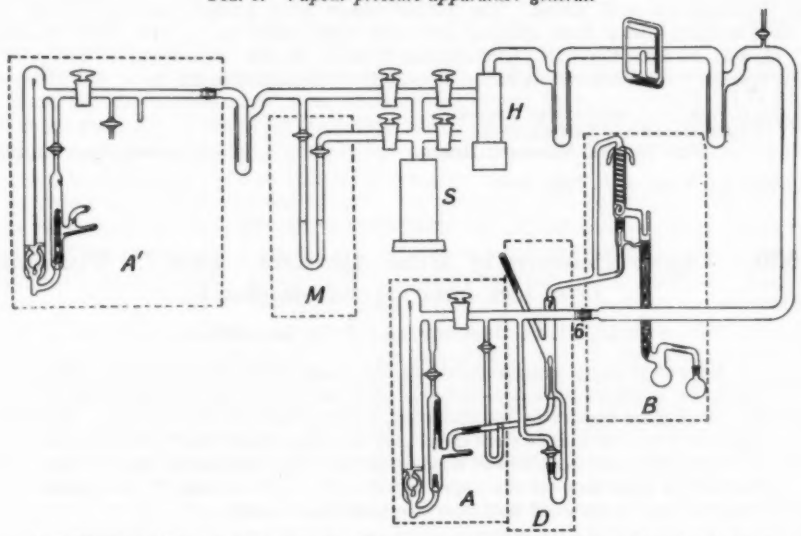
XUM

Experimental

Preparation of Titanium tert.-*Alkoxides.*—The *tert.*-butoxide and *tert.*-amyloxide were prepared by the methods described previously [1] from titanium tetrachloride which had been first refluxed over copper turnings (to remove vanadium) and then fractionally distilled. Although a conventional analysis for titanium established the purity of the compounds within 0·2% this was not a satisfactory criterion since a trace of volatile impurity could cause a large error in the vapour pressure. The reactivity of metal alkoxides precluded any chemical method of purification and it was necessary to devise physical methods (described below). Finally, it was decided that the best criterion was the establishment of a reproducible vapour pressure which did not alter whilst the sample was gradually evaporated. A special apparatus was developed during three years' studies and the final apparatus is described.

Apparatus.—General layout (Fig. 1). The sample was introduced at section *B* and distilled through the separator *D* into section *A* where it was isolated under a double-spoon gauge of

Fig. 1. *Vapour-pressure apparatus: general.*



S, " Speedivac " pump. H, mercury diffusions pump. For further explanation see text.

novel design. Section *A* was then transferred and attached (as *A'*) to the manometer section *M*. Here the sample was immersed in a thermostat, and its vapour pressure was determined by a null method. The apparatus was constructed entirely of " Pyrex " glass which was first cleaned with chromic acid, then washed, immersed in distilled water for 24 hr., and steamed for several hours. The assembled apparatus was then " outgassed " at about 10^{-5} mm. for several hours during which section *A* was heated at 300° and the rest of the apparatus was " flamed."

Section B (Fig. 2). A redistilled sample of alkoxide under an atmosphere of dry nitrogen in flask 1 was attached as shown in Fig. 2 and then distilled under a high vacuum into flask 2. The seal 3 was then " outgassed " and sealed-off. From this stage onward the alkoxide did not come into contact with any greased joints or taps and a high vacuum was maintained throughout. The sample was fractionally distilled at a high reflux ratio (40 : 1) which was controlled by the magnetically operated valve 4 which was ground into the seating 5. The column was packed with single-turn Fenske glass helices and was made adiabatic by an electrically heated jacket. This method of purification was adopted after extensive research on bulb-to-bulb vacuum-distillation had shown that the sealing-off procedure after each distillation actually introduced volatile impurities from the glass and the sample became

progressively less pure as determined by its vapour pressure. In fact the avoidance of contamination of the sample by traces of water and carbon dioxide liberated by molten glass proved to be a major problem (see section *A*). This experience is not new because Fairbrother *et al.*[4,5] had observed a similar difficulty in their work on the niobium and tantalum halides. The distillate from section *B* passed along a short inclined tube into the separator *D*.

Section D (Fig. 3). The distillate from *B* was caused to fall directly on to the thin finger-septum 2 by the drip-guide 1. The first runnings were thus made to run into the reservoir 3 which was cooled to *ca.* −78°. The magnetically controlled hammer 4 was used to break the septum and then withdrawn. The drip-guide was arranged so that the distillate then fell clear through the hole in the septum and thence ran into section *A* until the required sample had been collected. The final fraction was diverted into the reservoir 3 by placing the specially shaped end of the magnetic hammer over the hole in the septum.

Section A. This is shown in detail (except for the spoon gauge) in Fig. 4. The sample ran along from section *D* and dropped from the fixed drip-guide 2 on to another guide 3 which could be moved magnetically into a position which caused the alkoxide to fall clear through the standard (A.10) cone 4 into the spoon gauge compartment. The guide 3 was then withdrawn and the magnetically controlled standard (A.10) socket 5 was lowered on to the cone, thus isolating the pure sample. The residual film of alkoxide in the rest of section *A* was evaporated off and condensed in the trap 8 and the thickened glass at point 1 was outgassed at dull red-heat and then sealed off. With taps 7, 9, and 10 closed the apparatus was also sealed off below tap 9 and above tap 5 (Fig. 3), and section *A* was then placed at *A'* (Fig. 1). The new double spoon guage, described in the following Note, has a sensitivity of *ca.* 5 mm. deflection per mm. pressure difference, and a change of pressure of $<0{\cdot}01$ mm. Hg could thus be detected. The zero position was unaltered when the empty apparatus was heated to 300°.

Section M. The U-tube type of manometer with di-*n*-butyl phthalate as the manometric liquid is shown in Fig. 5. The limbs 1 and 2 were of " Veridia " precision bore (10 mm. diam.) to obviate surface tension effects and they were backed by a silvered glass scale (100 cm.) graduated in mm. The tubes and scale were mounted in a glass jacket (38 mm. diam.) containing a thermometer. Glass valves (3 and 4) were inserted above the tubes to prevent ejection of the manometric fluid by a sudden leak. Taps 5 and 6 could isolate the manometer tubes from the rest of the apparatus and it was necessary to include the reservoirs 7 and 8 to collect Silicone grease which drained out of the taps over a long period and thus avoid contamination of the manometric fluid. The bottom of the U-tube was joined to the oil reservoir 9 and the auxilliary taps 10, 11, 12, and 13. During use, the limb 1 was continuously evacuated through tap 5 to 5 microns pressure to eliminate traces of air which slowly diffused through the oil from the high-pressure side. During a measurement taps 6 and 10 were open, and 11, 12, and 13 closed, until the spoon gauge registered a deflection. This was balanced by introducing small quantities of dry air through 12 and 13. For small changes in level in the U-tube about 5 min. were allowed for drainage of the oil. The difference in levels was then read off (for pressures less than 10 mm. of Hg a travelling microscope was used). Tap 10 was then closed and by admission of more air through 12 and 13 or exhaustion through 11 the oil levels in 1 and 2 were simultaneously raised or lowered so that the pressure difference could be checked by using different parts of the U-tube. The di-*n*-butyl phthalate was purified by conventional methods and finally distilled *in vacuo*. Samples were taken at various times for density measurement.

The thermostat. The heating bath consisted of a 3-litre beaker filled with Silicone fluid (D.C.550). The thermoregulator was in the form of a helical coil which slid just inside the beaker and was made from tubing of external diam. 4 mm. (2·5 mm. bore) and was 4·5 m. long. The bottom was sealed off and the open end was joined to a vertical capillary (0·8 mm.). A Nichrome heating wire (250 w) was coiled evenly along the glass helix and the helix was supported on a glass framework made from 4 mm. rod which fitted into the clearance between the helix and the beaker. The helix was filled with mercury, and temperature control was effected by a " Sunvic " vacuum switch operated by the mercury regulator. An efficient paddle stirrer prevented temperature gradients, and the beaker was thermally insulated. Below 100° the temperature was constant within ±0·015° and above 100° no variation was detected by a thermometer reading to 0·1°. Temperatures were read to ±0·05° on a set of British Standard

[4] Alexander and Fairbrother, *J.*, 1949, 2472.
[5] *Idem*, *J.*, 1951, 3051.

XUM

thermometers of the partial-immersion type. A duplicate set which had been calibrated by N.P.L., Teddington, was kept for routine checking of the set in use.

FIG. 2. *Section B. Still for fractional distillation. Inset is the magnetic valve.*

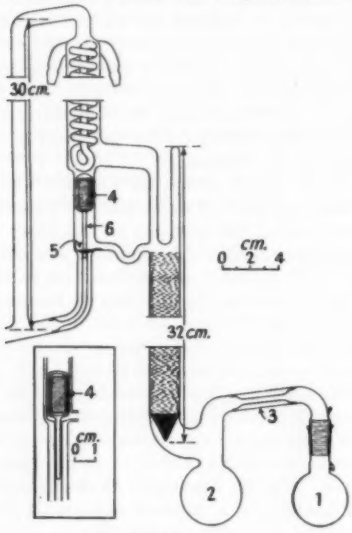


FIG. 3. *Section D. The separator.*

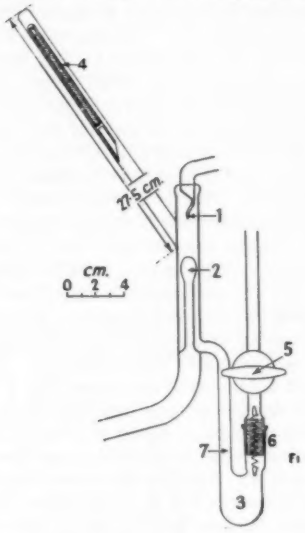


FIG. 4. *Section A.*

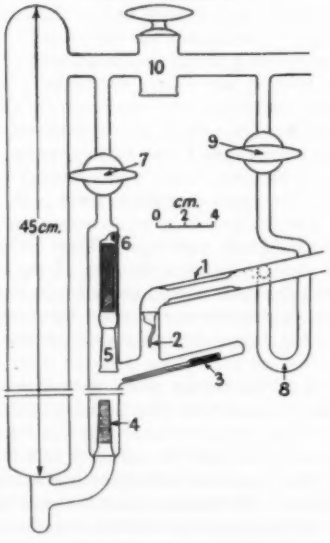
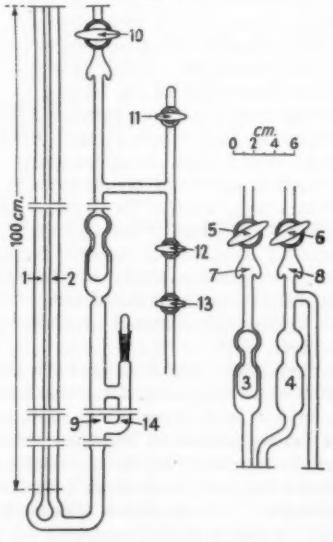


FIG. 5. *Section M. The oil manometer.*



Lubrication of joints. Tap no. 7 (Fig. 4) became hot during the outgassing process and during vapour pressure measurements at the higher temperatures. It was lubricated with Silicone high-vacuum grease, and a positive inward pressure was exerted on its key by a spring clip to prevent leakage. On all other taps and joints Apiezon M grease gave the best performance.

Tests for Purity.—The relative effect of a trace of volatile impurity in a sample of alkoxide is greatest at the lower vapour pressures and for this reason exhaustive tests for purity were carried out on samples at vapour pressures of *ca.* 0·050 mm. (*i.e.*, at about 30° for the *tert.*-butoxide and 70° for the *tert.*-amyloxide). With tap 7 and the A.10 joint (Fig. 4) closed the sample was allowed 20 min. at the appropriate temperature to reach equilibrium and the vapour pressure was then measured. The tap and joint were next opened and a portion of the sample was allowed to evaporate under a high vacuum. The sample was then isolated and its vapour pressure redetermined. This procedure was continued until all of the sample had evaporated. The sample was considered to be pure if it gave a constant vapour pressure throughout this procedure (except in the final stages when there was insufficient sample to give the saturated vapour pressure). The value of the vapour pressure thus determined was taken as the standard of purity by which to judge subsequent samples which were used for measurements over a wide temperature range. This criterion could be misleading if the impurity formed an azeotrope with the metal alkoxide, but in view of the analytical evidence and other considerations it seemed reasonable to rule out this possibility.

Measurement of Vapour Pressures.—Having established the purity of a sample at the low temperature, $T_1°$, a series of measurements were made at approximately 5° intervals in ascending order of temperatures over a range of about 30° up to, say $T_2°$. This was immediately followed by a descending series of measurements back to $T_1°$. The procedure was then repeated, but rising to a higher temperature $T_3°$ ($>T_2°$) followed by a return to $T_1°$. This somewhat laborious procedure was important for two reasons. First, the ascending-descending sequence would reveal by hysteresis any lag in attainment of equilibrium. Secondly, by raising the temperature in stages it was possible to approach the onset of decomposition without spoiling the sample too soon. Thus, if detectable decomposition had occurred at the high temperature $T_x°$ this would be revealed in the subsequent descent to $T_1°$. This is a major advantage of a static method of measurement over a dynamic method and proved invaluable in this work. One other feature of the technique remains to be described, namely, the prevention of leakage of sample through the A.10 cone and socket (Fig. 4). This could become serious at the higher vapour pressures and it was prevented by winding an auxiliary heating tape around the dead space between the socket and tap 7 in order to stop condensation of the very small quantity of alkoxide which slowly leaked through the cone and socket joint.

Results and Discussion

The results are presented as vapour pressures in mm. of mercury at 0° c (corrected for latitude and height above sea-level) and the temperatures are in degrees Kelvin. The temperature measurements are regarded as accurate within $\pm 0·05°$ and the pressures within $\pm 0·005$ mm.

When the results were plotted in the familiar form of log P against $1/T$, curvature was noted over the entire range investigated for both the *tert.*-butoxide and the *tert.*-amyloxide. The literature reveals at least fifty different vapour-pressure equations most of which are empirical, but the appearance of the curves for log P against $1/T$ suggested that the Kirchoff–Rankine equation might be applicable to our results and this equation has a theoretical basis. By following Frost and Kalkwarf's treatment [6] it can readily be shown that the Kirchoff–Rankine equation ($\ln P = a + b/T + c \ln T$, where a, b, and c are constants) can be rearranged into the following form containing two constants:

$$\ln (P/P_t) = b(1/T - 1/T_t) + c \ln (T/T_t) \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The parameters P_t and T_t correspond to any chosen experimental point. Equation (1) was further rearranged to the linear relation

$$Y = bX + c \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where $Y = \log (P/P_t)/\log (T/T_t)$, and $X = [(T_t - T)/TT_t]/2·3026 \log (T/T_t)$. The best straight line for equation (2) was determined by the least-squares method and the

[6] Frost and Kalkwarf, *J. Chem. Phys.*, 1953, **21**, 264.

XUM

constants b and c thus evaluated. The third constant a was deduced as follows. An arbitrary value of temperature T_n being used and T_t known, the function X was evaluated. The function Y for this value of temperature was then evaluated from the known values of X, b, and c. The value of the pressure P_n corresponding to the temperature T_n was deduced by solving the function Y. Finally, a was calculated by substituting the values of P_n, T_n, b and c in the original Kirchoff–Rankine equation. The main problem in this computation lies in making the correct choice of the arbitrary parameters P_t and T_t for there is no *a priori* method of selecting an experimental point which will be exactly on the line of best fit. In practice we adopted a graphical method of successive approximations to find the correct value of P_t and T_t starting from an experimental point in the high-pressure end of the results. This procedure was feasible because the linear equation (2) was found to be sensitive to the values of P_t and T_t and exhibited pronounced curvature when P_t was in error by more than *ca.* 1%. Satisfactory values of P_t and T_t were established by this graphical trial-and-error method. In principle the three-constant Kirchoff–Rankine equation can be solved by the least-squares method but with our data this was not possible because the constant c proved to be indeterminate.

The results for titanium *tert.*-butoxide and *tert.*-amyloxide are presented in Tables 1 and 2. The experimentally determined vapour pressures P are given in order of ascending temperature although two completely independent series of measurements were carried out on each compound. The values in parentheses were excluded from the above computation for the following reasons. Values below 0·3 mm. are liable to an error of *ca.* 3% in view of the estimated limit of ±0·005 mm. in the accuracy of measurements. On the other hand an error arises at the high-pressure end due to slight thermal decomposition and accordingly these values were excluded although the amount of decomposition was very small. The values of $P_{calc.}$ were obtained from the computed equation on the assumption that there was no error in the temperature reading.

Titanium Tetra-tert.-*butoxide.*—The computed results in Table 1 gave the equation:

$$\log P = 51{\cdot}0192 - 5278{\cdot}11/T - 14{\cdot}0219 \log T$$

For the 25 values used in the computation the percentage standard deviation $\sigma = (\Delta P)^2/(n-1)$ [where $\Delta P = 100(P_{calc.} - P/P_{calc.}$, and n = no. of observations] is 1·1%

TABLE 1. *Titanium tetra*-tert.-*butoxide.*

Temp. (K)	P (mm.)	$P_{calc.}$	Temp. (K)	P (mm.)	$P_{calc.}$	Temp. (K)	P (mm.)	$P_{calc.}$
299·1°	(0·039)	0·045	312·0°	(0·139)	0·135	352·2°	2·110	2·100
300·1	(0·036)	0·050	312·8	(0·147)	0·144	354·9	2·456	2·453
301·1	(0·049)	0·054	316·0	(0·188)	0·184	355·6	2·546	2·553
301·1	(0·051)	0·054	317·3	(0·198)	0·204	357·9	2·918	2·905
301·5	(0·046)	0·056	320·5	(0·269)	0·260	358·9	3·071	3·071
301·7	(0·055)	0·057	322·3	0·299	0·297	361·0	3·495	3·446
302·1	(0·056)	0·059	322·8	0·300	0·308	361·6	3·596	3·560
303·2	(0·067)	0·065	324·9	0·362	0·358	365·1	4·271	4·293
303·4	(0·062)	0·066	327·7	0·449	0·437	368·7	5·161	5·177
303·8	(0·064)	0·068	331·4	0·576	0·566	368·9	5·226	5·230
305·0	(0·078)	0·076	332·1	0·592	0·593	371·7	6·035	6·031
305·2	(0·078	0·077	334·9	0·707	0·716	382·3	10·11	10·06
305·3	(0·078)	0·078	335·1	0·737	0·726	387·7	12·82	12·87
306·5	(0·083)	0·086	338·5	0·907	0·907	393·6	(16·62)	16·66
307·9	(0·099)	0·097	345·6	1·405	1·417	398·1	(20·15)	20·14
308·5	(0·095)	0·101	347·3	1·583	1·571	402·1	(24·09)	23·72
309·1	(0·109)	0·107	349·5	1·788	1·792	409·1	(31·88)	31·23
309·5	(0·109)	0·110						

and corresponds to a probable error for any point of 0·74%. Moreover there are 15 changes of sign in the error ΔP in ascending this series of 25 points and this is in accordance with the requirements of a good statistical fit [7] to the proposed equation: *e.g.*, the number of

[7] Bond, "Probability and Random Errors," Arnold, London, 1935, p. 117.

changes of sign should be $\{(n - 1 + m)/2\} \pm 0{\cdot}34\sqrt{(n - 1 - m)}$, where n is the number of observation and m the number of constants in the equation. It is noteworthy that for the pressures at 402·1° and 409·1° the deviation $P - P_{calc.}$ agreed closely with the decomposition pressure calculated by applying the gas laws to the residual pressure found on returning to the low pressure region when the technique described in the Experimental section was used. Also, it is interesting to compare values of $P_{calc.}$ with the experimental results (in parentheses) in the low-pressure region. The agreement between P and $P_{calc.}$ is remarkably good and the standard deviation for the 23 points is 0·007 mm. with 11 changes of sign.

Titanium Tetra-tert.-*amyloxide*.—The computed results in Table 2 gave the equation:

$$\log P = 43{\cdot}1238 - 5472{\cdot}28/T - 11{\cdot}1706 \log T$$

TABLE 2. *Titanium tetra*-tert.-*amyloxide*.

Temp. (K)	P (mm.)	$P_{calc.}$	Temp. (K)	P (mm.)	$P_{calc.}$	Temp. (K)	P (mm.)	$P_{calc.}$
343·0°	(0·062)	0·071	385·3°	1·081	1·085	415·4°	5·014	5·017
343·7	(0·049)	0·074	388·5	1·291	1·297	416·8	5·344	5·349
345·6	(0·086)	0·086	388·9	1·321	1·326	421·1	6·485	6·495
346·2	(0·061)	0·089	391·4	1·541	1·519	423·0	7·065	7·066
349·0	(0·111)	0·109	391·6	1·531	1·535	423·2	7·105	7·128
349·1	(0·078)	0·110	392·5	1·611	1·611	424·0	(7·494)	7·382
350·3	(0·108)	0·120	392·5	1·621	1·611	424·9	(7·906)	7·680
352·4	(0·147)	0·139	394·8	1·801	1·819	430·0	(9·917)	9·553
353·7	(0·141)	0·152	398·0	2·161	2·149	433·3	(11·33)	10·96
354·3	(0·149)	0·159	399·1	2·262	2·273	435·2	(12·28)	11·86
355·3	(0·179)	0·170	399·7	2·348	2·344	440·3	(15·19)	14·56
356·1	(0·161)	0·179	401·3	2·542	2·542	444·0	(17·51)	16·83
357·5	(0·193)	0·197	401·4	2·552	2·554	446·3	(19·19)	18·38
360·1	(0·207)	0·235	404·7	3·053	3·012	451·6	(23·64)	22·44
361·2	0·251	0·252	404·9	3·053	3·041	453·1	(25·01)	23·72
366·2	0·350	0·348	408·9	3·683	3·694	453·7	(25·58)	24·25
371·1	0·479	0·473	410·2	3·943	3·932	460·2	(32·58)	30·62
377·7	0·690	0·703	411·2	4·103	4·123	469·6	(45·20)	42·26
378·8	0·749	0·750						

The computation was carried out in the same manner as for the butoxide and the standard deviation for the 28 points involved was ±0·66%, corresponding to a probable error for any point of ±0·44%. The number of changes of sign of ΔP in ascending the series was 12 which is close to the statistical requirement of 15 ± 2 for a random distribution of errors. Comparing the observed vapour pressures (in parentheses) at the low-pressure end of the series with those calculated from the vapour-pressure equation shows that the observed values are mainly lower than the calculated. However, in view of the probable error in the measurements in this region the agreement is good. For the 14 points involved the standard deviation is ±0·017 mm. with 8 changes of sign (cf. 8 ± 1 sign changes required for random distribution). It seems reasonable to suggest that vapour pressures in the temperature range 340—360° K may be calculated by extrapolation of the vapour-pressure equation with greater precision than we have been able to measure them. The data in parentheses in the higher-pressure region show some interesting features. The experimental vapour pressures are all higher than calculated, and the deviation increases with rise in temperature. In fact, as shown in Fig. 6, there is a striking correlation between the % deviation from the calculated and the % of $P_{obs.}$ due to volatile products of decomposition. This suggests the simple relation: $P_{calc.} = P_{obs.} - \delta$, where δ is the partial pressure of volatile products of decomposition measured in the manner already mentioned. Accordingly we suggest that vapour pressures in the temperature range 425—470° K may be reliably calculated by extrapolation of the vapour-pressure equation. Concerning the thermal decompositions at the higher temperatures we should point out that even at the highest temperatures studied no increase in pressure was detected during the time taken in making a pressure measurement and hence the decomposition was slow.

XUM

Nevertheless, during the longer time interval involved in changing from one temperature to the next a significant quantity of decomposition products could accumulate and was detected by the procedure already outlined. Finally we emphasize that in the computation of the vapour-pressure equation all the experimental results are taken in the temperature

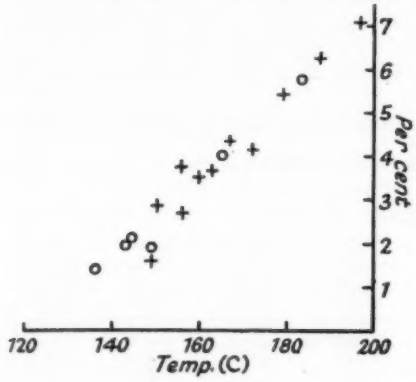


FIG. 6. *Correlation of thermal decomposition and deviation of vapour pressure from calculated values, for titanium tetra-*tert.*-amyloxide.*

○, *Percentage of* $P_{obs.}$ *due to residual gas.*
+, *Deviation of* $P_{obs.}$ *from calculated curve.*

region in which no decomposition was detected even by the very sensitive method of measuring the residual pressure at low temperature.

We thank the D.S.I.R. for a Maintenance Allowance (to J. D. S.) during the early stages of this work and also A.E.R.E., Harwell, for support in the later stages. We are indebted to Professor W. Wardlaw, C.B.E., for providing facilities for this research and for his interest and encouragement throughout its course.

BIRKBECK COLLEGE, MALET STREET, W.C.1. [*Received, February 10th,* 1958.]

NOTES.

651. *A New Double Spoon Gauge.*

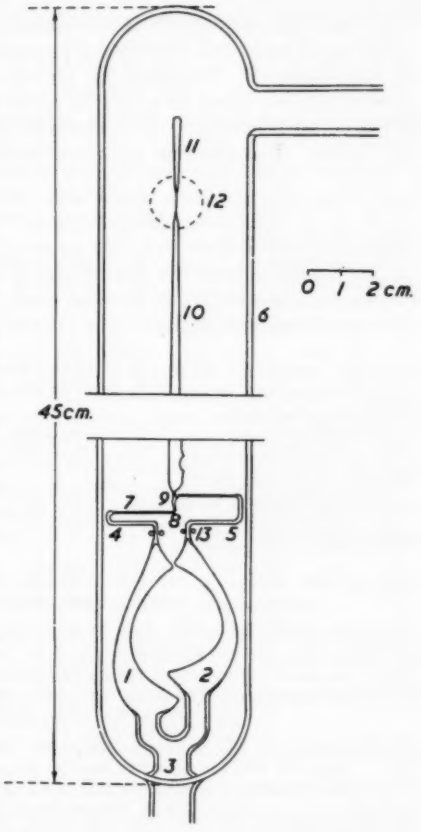
By J. D. SWANWICK.

SINCE the introduction [1] in 1906 of the first glass Bourdon gauge, there have been many developments of spoon, spiral, and diaphragm gauges,[2] in general suitable only for measurement of pressures above 10^{-1} mm. Hg.

Studies on the vapour pressures of the alkoxides [3] required a Pyrex-glass gauge capable of detecting pressure differences down to 10^{-2} mm. Hg and sufficiently robust to withstand cleaning with liquid reagents. If the sensitivity of a gauge is defined as the ratio of the deflection of the pointer to the applied pressure difference across the gauge, it was the author's experience that a sensitivity of about 3 mm. per mm. Hg was the optimum for a single spoon gauge with a mechanical pointer. Less sensitive gauges did not allow accurate pressure measurements, and more sensitive gauges were difficult to make and more easily broken both by normal manipulation and by small pressure differences to which such a gauge was temporarily subjected during actual pressure measurements. Spiral gauges are more robust than spoon gauges but are very difficult to clean.

[1] Ladenburg, *Verhandl. deutsch. phys. Ges.*, 1906, **8**, 20.
[2] Cf. Swanwick, Ph.D. Thesis, London, 1956.
[3] Bradley and Swanwick, preceding paper.

The new double spoon gauge now reported (see Figure) has a sensitivity 8—10 times that of the single spoon gauges used in its construction; the lever principle is adapted to the relative movement of two opposed spoon gauges, by causing the fulcrum of the lever-type pointer to move in the opposite direction to the applied force.



The two spoon gauges 1 and 2 communicate with each other and with the vaporisation chamber through the tube 3. Rigid glass supports 4 and 5 of diameter 1 mm. are sealed to the gauges, extending in the line of movement of the gauges to within about 1 mm. of the wall of the jacket 6. The support 4 carries a glass fibre 7 which is sealed to the lower extremity 8 of the pointer, and support 5 is likewise connected to the fulcrum 9. A thickness of 0·13 mm. for the fibres gave a suitable compromise between flexibility and strength. The pointer 10 (length 25 cm.) had to be made of minimum weight consistent with rigidity, and the optimum value was found to be *ca.* 20 mg. A fixed pointer was sealed to the upper end of the jacket, and the extremities of both pointers were drawn out to short fibres, the thickness of which was arranged to appear similar to the thickness of the scale divisions on the objective of the telescope 12 through which they were viewed. The optimum distance of the fulcrum from the lower end of the pointer was found to be about 5 mm., the gauge losing sensitivity as this distance was increased and a shorter distance resulting both in failure of the suspension system to support the pointer in a vertical position and in loss of sensitivity due to the finite rigidity of the horizontal connecting fibres.

Gauges with a sensitivity between 5 and 8 mm. per mm. Hg were satisfactory for a pressure difference of 10^{-2} mm.

A drawback of a spoon gauge is its inability to withstand large pressure differences, although this has been partially overcome in the double spoon gauge by the incorporation of four parallel horizontal bars 1 mm. in diameter, shown in end section (13) in the Figure, and placed so that the traverse of the spoon gauges was limited to less than 0·5 mm. Gauges capable of withstanding a pressure difference as great as one atmosphere have not been constructed but it is evident that stronger gauges will be considerably easier to assemble.

Two rigid glass supports (diam. 2—3 mm.) were sealed on to the tube 3 at their lower end and terminated at their upper end in a ring about 10 mm. in diameter held ~10 mm. below the upper extremity of the pointer. This ring and its supports (not shown in the Figure) were not essential to the working of the gauge but were helpful in the delicate process of inserting and sealing the gauge assembly into the glass jacket.

The double spoon gauge was very stable when subjected to vibration and was superior in this respect to single spoon gauges of similar sensitivity. This property is due to the opposing glass fibres which also absorb sudden shocks which would fracture a conventional gauge.

Birkbeck College, Malet St., London, W.C.1. [*Received, March 24th,* 1958.]

XUM

652. *Vinylanthracenes, and the Polymerization of the 9-Isomer.*

By Ernst D. Bergmann and Dov Katz.

The use of fluorescent substances embedded in a non-fluorescent polymer for scintillation counters led us to seek a method of preparing polymers which contained fluorescent radicals in their *molecule*. Studying the vinylanthracenes (1-, 2-, and 9-), their polymers, and co-polymers we have, in principle, achieved our aim. Vinylanthracenes have also been prepared by Hawkins.[1] The constants and spectra of our compounds are summarized in the Table. The addition of a conjugated ethylenic bond in the 2- or 9-position of

	R.S.*	M. p.	Found (%) C	Found (%) H	Required (%) C	Required (%) H	Colour †	Fluor.‡
Oximes ($C_{16}H_{13}NO$) § of								
9-acetylanthracene	E	185—186°	81·9	5·7	81·7	5·6	Y	Y
1-acetylanthracene	E	162—163	81·6	6·0	81·7	5·6	YB	LB
2-acetylanthracene	E	247—248	82·1	5·4	81·7	5·6	Y	LB
1-x′-*Anthrylethanols* ($C_{16}H_{14}O$) ‖								
$x = 9$	E,B	121—122	86·8	6·3	86·5	6·3	C	DB
$x = 1$	E	114—115	86·3	6·5	86·5	6·3	PY	LB
$x = 2$	E	156—157	86·5	6·4	86·5	6·3	PY	GB
Acetates ($C_{18}H_{16}O_2$) of								
1-9′-anthrylethanol	E	99—100	82·1	6·4	81·8	6·1	C	DB
1-2′-anthrylethanol	M	126—127	82·3	6·1	81·8	6·1	C	B
Benzoates ($C_{23}H_{18}O_2$) of								
1-9′-anthrylethanol	E	88—89	84·2	5·7	84·6	5·6	C	DB
1-2′-anthrylethanol	E	157—158	84·0	5·6	84·6	5·6	C	B
Vinylanthracenes ($C_{16}H_{12}$) ‖								
9-	M	64—65	93·8	5·8	94·1	5·9	Y	LY
1-	E	62—63	94·2	5·9	94·1	5·9	Y	LB
2-	E	186—187	93·5	6·2	94·1	5·9	Y	GY

Spectra: Ultraviolet (in ethanol) [mμ (log ε)]; infrared (KBr discs); fluorescence (in ethanol).

1-Vinylanthracene ... 255 (5·15), 369 (3·86), 390 (3·76). ν(C=CH_2) 990, 910 cm.$^{-1}$. Fluor. 410 mμ (m), 427 mμ (s), 455 mμ (m).

2-Vinylanthracene ... 220 (4·26), 258 (4·79), 266 (4·93), 277 (5·04), 314 (3·32), 328 (3·54), 345 (3·75), 362 (3·86), 383 (3·72). ν(C=CH_2) 990, 910 cm.$^{-1}$. Fluor. 408 mμ (m), 426 mμ (m).

9-Vinylanthracene ... 218 (4·00), 223 (4·00), 256 (5·25), 350 (3·70), 368 (3·85), 388 (3·78). ν(C=CH_2) 990, 933 cm.$^{-1}$. Fluor. 430 mμ (s).

1-1′-Anthrylethanol... 254 (5·08), 327 (3·42), 344 (3·20), 362 (3·87), 381 (3·81). ν(C–OH) 3226 cm.$^{-1}$. Fluor. 384 mμ (w), 408 mμ (s), 433 mμ (w).

1-2′-Anthrylethanol ¶ 256 (5·26), 325 (3·45), 340 (3·67), 357 (3·79), 376 (3·70). ν(C–OH) 3249 cm.$^{-1}$. Fluor. 409 mμ (m).

1-9′-Anthrylethanol... 256 (5·18), 327 (3·11), 332 (3·45), 348 (3·74), 366 (3·90), 386 (3·90). ν(C–OH) 3247 cm.$^{-1}$. Fluor. 393 mμ (w), 412 mμ (s), 437 mμ (w).

* Recrystallizing solvent: E, ethanol; B, benzene; M, methanol.

† Y, yellow; YB, yellow-brown; PY, pale yellow; C, colourless.

‡ Y, yellow; B, blue; L, light; D, dark; GB, greenish blue; GY, greenish yellow (fluorescence excited at 2537 Å).

§ Described by Martynoff,[2] after submission of this paper.

‖ Described by Hawkins.[1]

¶ The infrared spectra of 1-2′-anthrylethanol and its acetate show an indication of the presence of 2-vinylanthracene; this may be due to the pressure applied in the preparation of the potassium bromide pellet causing some dehydration.

anthracene changes the fluorescence from blue to yellow, but 1-vinylanthracene retains the blue fluorescence of anthracene. The hydroxyl frequency in 1-1′-anthrylethanol is lower than that of the 2′- and 9′-isomers; this may be due to the hydroxyl group's entering the field of the π-electrons of the middle ring. A similar phenomenon was observed by Anet and Bavin [2] for 9-(hydroxyalkyl)fluorenes.

[1] Hawkins, *J.*, 1957, 3858.

[2] Anet and Bavin, *Canad. J. Chem.*, 1956, **34**, 1756; Goldman and Crisler, *J. Org. Chem.*, 1958, **23**, 751.

[3] Martynoff, *Bull. Soc. chim. France*, 1958, 164.

The polymerizations were concerned mainly with 9-vinylanthracene. Radical polymerization (induced by benzoyl peroxide) is very slow, but copolymerization with styrene is quicker, the anthracene derivative inhibiting the polymerization of styrene. As the copolymer shows the typical blue fluorescence of anthracene we assume that its carbon backbone carries $C_{14}H_9$ (and C_6H_5) side groups.

The quantity of the anthracene derivative in the copolymer can be determined by comparison of the intensities of the ultraviolet absorptions at 262 mμ for the copolymer, anthracene, and polystyrene. Thus, when the original mixture contained 25% (w/w) of 9-vinylanthracene, the copolymer contained 4·5% of it.

The cationic polymerization of 9-vinylanthracene with stannic chloride as catalyst is very fast. If small quantities of catalyst are used, one obtains a soluble polymer of pure blue fluorescence, and with larger amounts of the catalyst insoluble products of slight yellow fluorescence are obtained. It can be assumed that the former is a pure vinyl polymer and the latter contains cross-links which involve the anthracene nuclei. In no case have the vinyl bands (at 990 and 933 $cm.^{-1}$) been detected in the infrared spectrum of the polymers, and their ultraviolet spectrum is identical with that of anthracene.

Experimental.—*1- and 2-Acetylanthracene.* Gore's method [4] was used; generally the ratio of anthracene : acetyl chloride : aluminium chloride was 1 : 3 : 3 and benzene was used as diluent (300 ml. for 45 g. of anthracene). The aluminium chloride was added, with stirring, at −3°, and the reaction continued for 1 hr. at about 5° and for 25 hr. at room temperature. After decomposition with ice and concentrated hydrochloric acid (1 : 1) the product was treated *in vacuo* to remove acetophenone and dissolved in boiling benzene. Upon cooling, 2-acetylanthracene crystallized; the 1-isomer was isolated by evaporation of the mother liquor and recrystallization of the residue from light petroleum (b. p. 60—90°) (total yield, 41%; ratio of 2 : 1-acetylanthracene, 1 : 4).

The three acetylanthracenes were reduced with lithium aluminium hydride in ether (1- and 9-compound) or tetrahydrofuran (2-compound) (yield, 80, 95, and 100% respectively).

Vinylanthracenes.—The 1-*x*-anthrylethanol (5 g.) was heated with potassium hydrogen sulphate (0·25—0·5 g.) and copper powder (0·05—0·1 g.) at 1 mm. pressure. The products distilled at 160—170°. 9-Vinylanthracene (yield, 85—90%) was recrystallized from methanol, the other two isomers (yields, 60—65 and 65—70%) from ethanol. The addition of copper powder to the dehydration mixture reduced the tendency to polymerization.

Polymerizations.—9-Vinylanthracene (0·4 g.) and benzoyl peroxide (0·016 g.) were sealed in glass tubes at 1 mm. pressure and heated at 90° for 48 hr. and then at 110° for 20 days. (The polymerization was, therefore, initially catalyzed, but in the later stages thermal.) After this time, the product was solid at 110°. It was dissolved in benzene and the yellowish polymer precipitated with methanol (softening point, 220—230°).

9-Vinylanthracene and styrene were copolymerized by the same technique (with 2% of benzoyl peroxide). The reaction is catalytic only in its first stages. The mixture was heated for 48 hr. at 90° and then at 110° until, upon cooling, the mass broke up or separated from the walls, owing to the reduction in molar volume of the polymer. When the amount of vinyl anthracene in the mixture was raised from 0 to 1, 5, 10, and 25% (by weight), the polymerization time increased from 2 hr. to 48, 72, 72, hr., and 107 days, respectively, and the conversion decreased from 97 to 97, 92, 83, and 61%, respectively.

For cationic polymerizations, 9-vinylanthracene (0·75 g.) was mixed with 0·75 g. of anhydrous benzene, and an aliquot part of a 38% solution of stannic chloride in benzene was added at 20°. When the concentration of the chloride in the mixture was 0·15% and 0·25%, viscous, yellow solutions were obtained, the conversions being 14 and 40%, respectively. Also, with 0·5% of stannic chloride, a very viscous solution was obtained. At higher concentrations of the catalyst (1·0 and 2·5%), the polymer was a dark-brown insoluble solid, which was precipitated after 10 and 2 min., respectively. The first soluble polymer shows a pure blue fluorescence (437 mμ in chloroform), and a spectrum practically identical with that of anthracene.

SCIENTIFIC DEPARTMENT, ISRAEL MINISTRY OF DEFENCE. [*Received, January 23rd*, 1958.]

[4] Gore, *J. Org. Chem.*, 1957, **22**, 135.

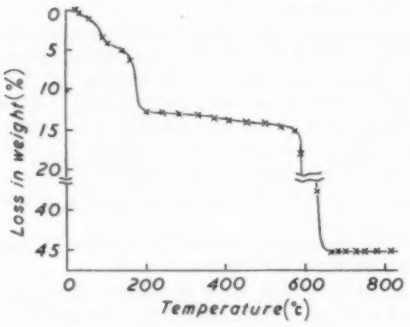
XUM

653. *The Preparation and Properties of Some Plutonium Compounds. Part VIII.* Plutonium*(IV) *Sulphate.*

By J. L. Drummond and G. A. Welch.

Cunningham,[1] and Harvey, Heal, Maddock, and Rowley,[2] reported that anhydrous plutonium(IV) sulphate was obtained by evaporating dilute sulphuric acid solutions of quadrivalent plutonium salts, followed by gentle ignition to remove the excess of acid; also that it was stable in air and could readily be weighed as such. It was soluble in dilute mineral acids, but deposited crystals of the tetrahydrate from concentrated solutions in sulphuric acid. Anderson[3] precipitated the same hydrate by adding methanol to the solution, and found that if the hydrate was dried in air at 153° then $Pu(SO_4)_2,\frac{1}{2}H_2O$ was formed. Further heating at 280° decomposed it to a basic sulphate and ignition at 800° entirely to the dioxide. Allison[4] found that the anhydrous salt has a $Pu : SO_4$ weight ratio of 1·26 compared with the theoretical value of 1·24, but recommended it as a gravimetric standard.

Thermogravimetric curve of plutonium(IV) *sulphate.*



While seeking a suitable gravimetric standard for plutonium, we studied the preparation, composition, and stability of the quadrivalent sulphate. The anhydrous salt was prepared from specially purified plutonium nitrate solutions by repeated evaporation and fuming with sulphuric acid. The sulphate was heated in an open container at a fixed temperature between 450° and 650°, the thermal stability range quoted by Dawson and Elliott[5] from thermogravimetric data. The product was hygroscopic, and even when cooled in dry air and weighed in a closed weighing bottle it was not possible to attain constant weight. There was a steady loss of 0·1—0·2% per 15 minutes' heating at any temperature, or a more pronounced loss if the temperature was raised. Therefore, samples were weighed after being heated at the desired temperature for 15 min. only. The plutonium content was determined by ignition to 870° to form the oxide[6] $PuO_{2\cdot09}$, and the weight ratio of plutonium sulphate : plutonium oxide was calculated. The mean ratios obtained, with their spread, from the number of determinations shown in parentheses at given temperatures, were: 450° (2), 1·600 ± 0·003; 480° (5), 1·592 ± 0·002; 490° (4), 1·588 ± 0·004; 510° (2), 1·584 ± 0·001; 520° (8), 1·583 ± 0·005; 570° (2), 1·569 ± 0·002. They thus vary with the temperature of preparation of the sulphate on both sides of the theoretical ratio of 1·582. The variation was confirmed by careful examination of the compound on a sensitive thermobalance; the heat-stability curve of plutonium sulphate containing a little free acid is in the Figure. Thus the anhydrous sulphate is not a suitable weighing form for plutonium gravimetry.

In some preparations, the plutonium sulphate contained yellow patches which were converted into the normal pink form by repeated fuming to dryness with sulphuric acid. The yellow material was believed to be plutonyl sulphate, as it was soluble in water and

* Part VII, *J.*, 1957, 4785.

[1] Cunningham, "The Actinide Elements," McGraw-Hill Book Co. Inc., New York, 1954, p. 408.
[2] Harvey, Heal, Maddock, and Rowley, *J.*, 1947, 1010.
[3] Anderson, "The Transuranic Elements," McGraw-Hill Book Co. Inc., New York, 1949, p. 796.
[4] Allison, Report P.D.B.-60 (Atomic Energy of Canada Ltd.).
[5] Dawson and Elliott, A.E.R.E. C/R. 1207 (U.K. Atomic Energy Authority).
[6] Drummond and Welch, *J.*, 1957, 4781.

was not formed if plutonium(VI) was absent originally. However, the maximum yield of this material was about 10%, even from pure plutonyl nitrate.

Anhydrous plutonium(IV) sulphate was soluble in 5N-mineral acids, although crystals of a less soluble hydrate were sometimes deposited on standing. It also dissolved in water. An approximately 0·5M-aqueous plutonium sulphate solution was stable, but a 0·05M-solution became cloudy after 1 hr. More dilute solutions rapidly became turbid and the plutonium which was not precipitated was probably colloidal. Thus the stability of a solution of plutonium sulphate in water, and to some extent in dilute sulphuric acid, depends upon the concentration of the salt, probably owing to formation of an anionic complex by the sulphate ions liberated by partial hydrolysis, thus preventing complete hydrolysis. A stable solution of plutonium sulphate in water was shown to contain much anionic and negligible cationic plutonium by electromigration.

Experimental.—Anhydrous plutonium(IV) *sulphate.* Pure plutonium nitrate solutions (0·2—0·5 g. of Pu), mixed with sulphuric acid (0·5—1 ml. of 18N) and a little sulphur dioxide water to reduce any plutonium(VI), were evaporated to dryness in small tared silica weighing bottles and heated at fixed temperatures between 450° and 570° for 15 min. The bottles were covered and cooled in dry air and weighed on a semimicro balance. The plutonium sulphate was then moistened with 18N-sulphuric acid and heated at the same temperature until the weight was constant to within 0·1%.

The silica spiral thermobalance has been described.[7]

Acknowledgment is made to Heather M. Ockenden for the thermogravimetry, and to Sir Leonard Owen, the Managing Director of the Industrial Group of this Authority, for permission to publish this note.

U.K. Atomic Energy Authority, Dounreay Experimental Reactor Establishment, Dounreay, nr. Thurso, Caithness. [*Received, March 7th*, 1958.]

[7] Brown, Ockenden, and Welch, *J.*, 1955, 3932.

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654. *Solvated Triphenylmethane Derivatives containing Bromine.*

By J. E. Driver and (Miss) T. F. Lai.

Triphenylmethane derivatives which form molecular compounds with hydrocarbon and chlorohydrocarbon solvents were described by Driver and Mok.[1] Mr. H. M. Powell suggested that solvated compounds of this type containing bromine might be particularly suitable for crystallographic study, and the examples tabulated have therefore been prepared.

Compound (*A*)			Solvent (*B*)	*A* : *B* (mols.)	Compound (*A*)			Solvent (*B*)	*A* : *B* (mols.)
Br	OH	Me			Br	OH	Me		
3	4′ : 4″	—	Benzene	1 : 1	3	2′ : 2″	5′ : 5″	*p*-Xylene	2 : 1
			Toluene	1 : 1	3	4′ : 4″	3′ : 3″ : 5′ : 5″	Benzene	1 : 1
3	4′ : 4″	3′ : 3″	*p*-Xylene	1 : 1	4	4′ : 4″	—	Benzene	2 : 3
3	4′ : 4″	2′ : 2″	Benzene	1 : 1	4	4′ : 4″	3′ : 3″ : 5′ : 5″	Benzene	3 : 2
			p-Xylene	1 : 1	2	4′ : 4″	—	Benzene	*ca.* 1 : 1
			Chlorobenzene	1 : 1					
			Bromobenzene	1 : 1					

Experimental.—Phenols, bromobenzaldehydes, hydrocarbons, and halogenohydrocarbons were suitably purified, and distilled within 1° or had sharp m. p.s. Microanalyses are by Dr. Zimmermann, Melbourne.

3-Bromo-4′ : 4″-dihydroxytriphenylmethane. A solution of *m*-bromobenzaldehyde (9·2 g.) and phenol (10·4 g.) in acetic acid (10 ml.) was cooled to 0°, and sulphuric acid (3 ml.) in acetic acid (10 ml.) was added dropwise with stirring. The mixture was kept at *ca.* 0° for 16 hr. and then stirred into crushed ice. The orange solid (17 g.) crystallized as the *benzene compound*

[1] Driver and Mok, *J.*, 1955, 3914.

XUM

in pale yellow needles which melted at 156—157° with loss of solvent (Found: loss at 132°/3 mm., 17·3. $C_{19}H_{15}O_2Br,C_6H_6$ requires C_6H_6, 18·0%). The *toluene compound* softened at 110—120° with loss of solvent (Found: loss at 132°/3 mm., 20·8. $C_{19}H_{15}O_2Br,C_7H_8$ requires C_7H_8, 20·6%). The unsolvated *compound* separated from chlorobenzene or bromobenzene in stout, yellow prisms, m. p. 159—160°, though under some conditions solvated crystals were formed from these solvents (Found: C, 64·3; H, 4·4; Br, 22·4%; *M*, 362. $C_{19}H_{15}O_2Br$ requires C, 64·2; H, 4·2; Br, 22·5%; *M*, 355). The *dibenzoyl derivative* separated from light petroleum in needles, m. p. 164—165° (Found: C, 70·6; H, 4·4; Br, 13·9%; *M*, 618. $C_{33}H_{23}O_4Br$ requires C, 70·3; H, 4·1; Br, 14·2%; *M*, 563).

3-Bromo-4′ : 4″-dihydroxy-3′ : 3″-dimethyltriphenylmethane was prepared from *m*-bromobenzaldehyde (9·2 g.) and *o*-cresol (11·9 g.) (7 days). The product (15 g.) yielded the *p-xylene compound* by slow crystallization as large, pale yellow plates which melted at 60—65° with loss of solvent (Found: loss at 132°/3 mm., 21·0. $C_{21}H_{19}O_2Br,C_8H_{10}$ requires C_8H_{10}, 21·7. Found, for the unsolvated compound: C, 65·9; H, 5·4; Br, 19·9%; *M*, 352. $C_{21}H_{19}O_2Br$ requires C, 65·8; H, 5·0; Br, 20·9%; *M*, 383).

3-Bromo-4′ : 4″-dihydroxy-2′ : 2″-dimethyltriphenylmethane was prepared from *m*-bromobenzaldehyde (4·5 g.) and *m*-cresol (6 g.) (18 hr.). The product (7·5 g.) yielded the *benzene compound* in needles, m. p. 216—218° (decomp.) (Found: loss at 100°/3 mm., 17·0. $C_{21}H_{19}O_2Br,C_6H_6$ requires C_6H_6, 16·9%). The unsolvated compound, made by heating the benzene compound at 100°/3 mm., melted at 220—221° (decomp.) (Found: C, 66·0; H, 5·1; Br, 20·4%; *M*, 400). The p-*xylene compound* formed pale yellow crystals, m. p. 218° (decomp.) (Found: loss at 132°/3 mm., 20·9%). The *chlorobenzene compound* formed yellow crystals, m. p. 210—212° (decomp.) (Found: loss at 132°/3 mm., 22·6. $C_{21}H_{19}O_2Br,C_6H_5Cl$ requires C_6H_5Cl, 22·7%). The *bromobenzene compound* melted at 215—216° (decomp) (Found: loss at 155°/3 mm., 28·6. $C_{21}H_{19}O_2Br,C_6H_5Br$ requires C_6H_5Br, 29·1%).

3-Bromo-2′ : 2″-dihydroxy-5′ : 5″-dimethyltriphenylmethane was prepared from *m*-bromobenzaldehyde (4·5 g.) and *p*-cresol (6 g.) (18 hr.). The crude product (7·5 g.) was extracted with sodium hydroxide solution. Acidification with hydrochloric acid gave a brown resin, which yielded the p-*xylene compound* in colourless plates, m. p. 140—144° with loss of solvent (Found: loss at 132°/3 mm., 12·0. $2C_{21}H_{19}O_2Br,C_8H_{10}$ requires C_8H_{10}, 12·2%). The unsolvated compound, prepared by heating the *p*-xylene compound at 132°/3 mm., melted at 155—157° (Found: C, 66·2; H, 5·1; Br, 18·6%; *M*, 410).

3-Bromo-4′ : 4″-dihydroxy-3′ : 3″ : 5′ : 5″-tetramethyltriphenylmethane was prepared from *m*-bromobenzaldehyde (4·6 g.) and 2 : 6-xylenol (6·6 g.) (48 hr.). The orange product (10 g.) yielded the *benzene compound* in pale yellow crystals which softened at *ca.* 100° with loss of solvent (Found: loss at 100°/4 mm., 16·2. $C_{23}H_{23}O_2Br,C_6H_6$ requires C_6H_6, 16·0%). The unsolvated compound melted at 140—142° (Found: C, 67·4; H, 5·7; Br, 19·5%; *M*, 417. $C_{23}H_{23}O_2Br$ requires C, 67·2; H, 5·6; Br, 19·5%; *M*, 411).

4-Bromo-4′ : 4″-dihydroxytriphenylmethane was prepared from *p*-bromobenzaldehyde (1·5 g.) and phenol (1·7 g.) (72 hr.). The product (2·5 g.) yielded the *benzene compound* in pale yellow crystals which melted at 98° with loss of solvent (Found: loss at 100°/4 mm., 24·5. $2C_{19}H_{15}O_2Br,3C_6H_6$ requires C_6H_6, 24·8%). The unsolvated compound melted at 124—126° (Found: C, 64·3; H, 4·4; Br, 22·9%; *M*, 397).

4-Bromo-4′ : 4″-dihydroxy-3′ : 3″ : 5′ : 5″-tetramethyltriphenylmethane was prepared from *p*-bromobenzaldehyde (2·3 g.) and 2 : 6-xylenol (3·3 g.) (18 hr.). The product (5 g.) yielded the *benzene compound* as pale orange needles which melted at 156—166° with loss of solvent (Found: loss at 100°/3 mm., 12·0. $3C_{23}H_{23}O_2Br,2C_6H_6$ requires C_6H_6, 11·2%). The unsolvated compound melted at 164—166° (Found: C, 67·3; H, 5·7; Br, 18·0%; *M*, 469).

2-Bromo-4′ : 4″-dihydroxytriphenylmethane was prepared from *o*-bromobenzaldehyde (2·3 g.) and phenol (2·6 g.) (time, 48 hr.). The benzene compound formed fine, white needles which softened at 120° with loss of solvent; the benzene content was variable and non-stoicheiometric (Found: loss at 100°/3 mm., 15·8; 14·6%). The unsolvated compound melted at 156—157° (Found: C, 65·4; H, 4·3; Br, 21·9%; *M*, 350).

We are grateful to Mr. H. M. Powell for his advice, and for making a preliminary examination of some of the compounds described in the previous paper.[1] One of us (T. F. L.) thanks the University of Hong Kong for a grant.

UNIVERSITY OF HONG KONG, HONG KONG. [*Received, March 17th,* 1958.]

655. *Properties and Reactions of Alkyl Free Radicals in Solution. Part XI.* Further Water-soluble Radicals.*

By R. M. Haines and William A. Waters.

In Part VIII [1] we described the preparation and decomposition of azo-nitriles obtained from lævulic and γ-oxopimelic acids, showing that the resulting free radicals had redox potentials E_{-e} of about +0·4 v. Attempts to make further water-soluble alkyl radicals are now reported. All are polymerisation catalysts with similar redox potentials. A more detailed study of the decomposition of azo-nitriles in water gives added support for the finding of Talât-Erben and Bywater [2] that some radical combination to keten-type intermediates RR'C(CN)·N:C:CRR' occurs, for 13% of an amide $Me_2C(CN)\cdot NH\cdot COPr^i$ has been isolated after decomposition of an aqueous suspension of αα'-azo*iso*butyronitrile, the yield of tetramethylsuccinonitrile being substantially less than that reported by Bickel and Waters [3] for the decomposition in toluene.

Experimental.—**1 : 1'-*Azobis*-2-*carboxymethyl*-1-*cyano*cyclo*pentanone*.** 2-Oxo*cyclo*pentyl-acetic acid,[4] m. p. 53°, was characterised as the *ethyl ester* **2 : 4-*dinitrophenylhydrazone***, m. p. 107° (Found: C, 51·7; H, 5·1; N, 15·8. $C_{15}H_{18}O_6N_4$ requires C, 51·6; H, 5·2; N, 16·0%). The acid (5·5 g.), neutralised in sodium carbonate solution, was gradually added to stirred sodium cyanide (2 g.) and hydrazine sulphate (2·6 g.) in water (25 ml.), the temperature being kept at 42—45° for 3 hr. The solution was then acidified with hydrochloric acid, cooled in ice, stirred rapidly, and oxidised gradually with bromine. After removal of the slight excess of bromine with sodium hydrogen sulphite the solution was stored at 0° and the solid mixture of isomeric azo-nitriles separated. This, on trituration with ether, gave a white solid, m. p. 156—160° (decomp.), with the requisite absorption spectra for an aliphatic *azo-nitrile* [4·5 (CN), 5·9 μ (CO of CO_2H), and 375 mμ (·N:N·)] [Found: C, 57·8; H, 6·3; N, 16·3%; equiv., 155. $C_{14}H_{18}N_4(CO_2H)_2$ requires C, 58·0; H, 6·0; N, 16·9%; equiv., 152].

2 : 2'-*Azobis*-2-*propionamidine dihydrochloride*. Dry hydrogen chloride was passed into αα'-azo*iso*butyronitrile (30 g.) in dry methanol (97 ml.) at 0° until the solution was saturated. After 24 hr. the excess of hydrogen chloride was removed under diminished pressure and dry ammonia was passed into the remaining suspension. After a further 2 days' storage at 0° the excess of ammonia was removed similarly. Solid (20 g., m. p. >210°) was separated, dissolved in the minimum volume of cold water, and treated with saturated sodium chloride solution, which precipitated the pure *amidine hydrochloride*, leaving ammonium and sodium chloride in solution. The product was very soluble in water, but insoluble in ether, acetone, or chloroform (Found: C, 35·7; H, 7·8; N, 30·2; Cl, 25·7. $C_8H_{20}N_6Cl_2$ requires C, 35·4; H, 7·4; N, 31·0; Cl, 26·2%), $\lambda_{max.}$ 370 and 210 mμ. The free base was not stable.

2 : 2'-*Azobis*-2-*butyramidine dihydrochloride*, prepared similarly, in ethanol, from 2 : 2'-azobis-2-cyanobutane [5] (47% yield; decomp. above 200°), had $\lambda_{max.}$ 368 and 211 mμ (Found: C, 39·2; H, 7·9; N, 27·2; Cl, 23·4. $C_{10}H_{24}N_6Cl_2$ requires C, 40·1; H, 8·0; N, 28·1; Cl, 23·7%).

From the decomposition of 2 : 2'-azobis-2-propionamidine hydrochloride (10 g.) in water (60 ml.) at 100° there was obtained a crystalline solid hydrochloride (1·4 g.), m. p. >270° (decomp.) (from moist ethanol), appearing from analyses to be **β-*carbamoyl*-αα*β*-*trimethylbutyramidine hydrochloride***, $H_2N\cdot CO\cdot CMe_2\cdot CMe_2\cdot C(:NH)\cdot NH_2,HCl$ (Found: C, 46·6; H, 8·9; N, 20·3; Cl, 16·8. $C_8H_{18}ON_3Cl$ requires C, 46·3; H, 8·7; N, 20·6; Cl, 17·1%); its *picrate*, from ethanol, had m. p. 258—260° (Found: N, 21·4. $C_{14}H_{20}O_8N_6$ requires N, 21·0%). Construction of a scale model of tetramethylsuccindiamidine hydrochloride was found to be spatially impossible: this substance could not be prepared in the normal way from tetramethylsuccinonitrile.

1 : 1'-Azobis-1-cyano-2-oxo*cyclo*pentylacetic acid and both the amidine hydrochlorides

* Part X, *J.*, 1958, 2056.

[1] Haines and Waters, *J.*, 1955, 4256.
[2] Talât-Erben and Bywater, *J. Amer. Chem. Soc.*, 1955, **77**, 3710, 3712.
[3] Bickel and Waters, *Rec. Trav. chim.*, 1950, **69**, 1490.
[4] Meade and Linstead, *J.*, 1934, 40.
[5] Ford and Waters, *J.*, 1951, 1851.

XUM

were, when heated in aqueous solution under nitrogen or carbon dioxide, catalysts for the polymerisations of vinyl cyanide, vinyl acetate, and methyl methacrylate. Their solutions had reducing properties analogous to those of the radicals described in Part VIII.[1] On checking our evidence however, we find that the acid vanadate is not reduced below the oxidation level of blue quadrivalent vanadium.

Attempts have been made to synthesise, from triacetonamine and from aromatic ketones, azo-nitriles containing solubilising groups, *e.g.*, OH, NH_2, NMe_2. This has not been successful but in the course of the work the following new compounds were obtained: the two azo-nitriles were polymerisation catalysts when tested in suspension in hot water.

Storage of *4-phenylbutan-2-one ketazine*, m. p. 40° (Found: C, 82·0; H, 8·2; N, 5·6. $C_{20}H_{24}N_2$ requires C, 82·2; H, 8·3; N, 9·6%), for 2 weeks in moist liquid hydrogen cyanide yielded crystals, m. p. 85—100° of stereoisomers of *3 : 3′-hydrazobis-3-cyano-1-phenylbutane* (Found: C, 76·2; H, 7·6; N, 16·1. $C_{22}H_{26}N_4$ requires C, 76·3; H, 7·6; N, 16·2%) which when oxidised, as above, with bromine in dilute hydrochloric acid gave mixed isomers, m. p. 85—95°, of *3 : 3′-azobis-3-cyano-1-phenylbutane* in 46% yield (calc. on ketone); a sample crystallised from ethanol had m. p. 110° (Found: C, 76·9; H, 7·5; N, 16·3. $C_{22}H_{24}N_4$ requires C, 76·7; H, 7·0; N, 16·3%). *4-p-Nitrophenylbutan-2-one azine*, m. p. 107—109° (Found: C, 62·2; H, 5·8; N, 14·4. $C_{26}H_{22}O_4N_4$ requires C, 62·8; H, 5·8; N, 14·7%), by a similar procedure gave impure 3 : 3′-azobis-3-cyano-1-*p*-nitrophenylbutane, m. p. 133—135° (decomp.) (Found: C, 61·8; H, 4·8. Calc. for $C_{22}H_{22}O_4N_6$: C, 60·8; H, 5·2%), but at atmospheric pressure addition of more than one molecule of hydrogen cyanide to the ketazines of *p*-hydroxyacetophenone, Michler's ketone, and triacetonamine could not be effected. The *triacetonamine azine*, from light petroleum (b. p. 40—60°), had m. p. 134° (Found: C, 70·7; H, 11·5; N, 18·3. $C_{18}H_{34}N_4$ requires C, 70·6; H, 11·2; N, 18·3%).

Decomposition of αα′-azo*iso*butyronitrile in boiling water has already received brief mention.[6] From 16·4 g. in 200 ml. of water it has been possible to isolate by filtration tetramethylsuccinonitrile, m. p. 169°, in *ca.* 65% yield, and 2 : 3 : 5-tricyano-2 : 3 : 5-trimethylhexane,[3] m. p. 82°, in 7·5% yield. Evaporation of the aqueous solution gave 1·8 g. (13%) of a solid, m. p. 108° (from benzene), that proved to be *N*-(1-cyano-1-methylethyl)*iso*butyramide (Found: C, 62·4; H, 9·2; N, 18·3. Calc. for $C_8H_{14}ON_2$: C, 62·3; H, 9·1; N, 18·1%), identical with material synthesised from α-amino*iso*butyronitrile and *iso*butyryl chloride. The analogous *N-(1-carbamoyl-3-carboxy-1-methylpropyl)-γ-carboxy-α-methylbutyramide*, m. p. 150° (from ethanol) (Found: C, 49·3; H, 7·1; N, 9·5. $C_{12}H_{20}O_6N_2$ requires C, 50·0; H, 6·9; N, 9·7%), was isolated in 20% yield on decomposition in water of 4 : 4′-azobis-(4-cyanopentanoic acid).[1] Its infrared spectrum had bands at 2·8—4·0 (OH), 2·9 and 3·0 (NH), 5·9 (CO of CO_2H), 6·1 and 6·35 μ (CO or CO·NH_2), and 6·6 μ (CO of ·CO·NH·).

One of us (R. M. H.) thanks the Department of Scientific and Industrial Research for a maintenance grant.

The Dyson Perrins Laboratory, Oxford University. [*Received, March 26th,* 1958.]

[6] Tilney-Bassett and Waters, *J.*, 1957, 3129.

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656. *Hydrogenation of 4-Hydroxyisophthalic Acid.*

By A. S. Lindsey.

An examination of the products of hydrogenation of 4-hydroxy*iso*phthalic acid was made as part of a study of the chemistry [1] and pharmacology of this compound.[2]

Preliminary experiments indicated that hydrogenation of diethyl 4-hydroxy*iso*phthalate over palladium [3] gave low yields. However hydrogenation of the alkali-metal salt in aqueous solution in the presence of Raney nickel catalyst [4] proceeded to approximately 70% completion.

[1] Hunt, Jones, and Lindsey, *J.*, 1956, 3099; Gladych, Lindsey, and Taylor, *J.*, 1957, 4834.
[2] Chesher, Collier, Robinson, Taylor, Hunt, Jones, and Lindsey, *Nature*, 1955, **175**, 206; Collier and Chesher, *Brit. J. Pharmacol.*, 1956, **11**, 20.
[3] Martin and Robinson, *J.*, 1943, 491.
[4] B.P. 353,373/1931: B.P. 366,244/1932.

One of the products, isolated in about 16% yield, was the previously unknown crystalline 4-hydroxy*cyclo*hexane-1 : 3-dicarboxylic acid, which was characterised by its infrared absorption spectrum and as its dimethyl ester. The non-crystalline portion of the hydrogenation product furnished *trans*-4-hydroxy*cyclo*hexanecarboxylic acid [5,6] and a *cyclo*hexene-1 : 3-dicarboxylic acid, which could also be obtained by treatment of the dimethyl 4-toluene-*p*-sulphonyl*cyclo*hexane-1 : 3-dicarboxylate with potassium *tert.*-butoxide in *tert.*-butyl alcohol and subsequent hydrolysis. The dicarboxylic acid is most likely to be the alkali-stable Δ^3-isomer (m. p. 244°) [7] and must arise through dehydration during either the hydrogenation or distillation.

Experimental.—General. Microanalyses were carried out by the microanalytical section of this laboratory. Infrared absorption spectra of solids dispersed in potassium chloride discs were measured on a modified Hilger D209 double-beam instrument; only the strong and medium strength bands are reported.

Preliminary Hydrogenation Experiments.—Attempts to hydrogenate diethyl 4-hydroxy-*iso*phthalate, dissolved in redistilled ethyl acetate, under the following conditions led to the recovery of approximately 90% of the starting material: (*a*) with 5% Pd on asbestos at 155—170° for 7 hr. under 136 atm. of hydrogen, (*b*) with 2% Pd on barium carbonate at 150—200° for 7 hr., under 125 atm. of hydrogen.

Hydrogenation of 4-Hydroxyisophthalic Acid over Raney Nickel.—A stirred solution of 4-hydroxy*iso*phthalic acid (100 g.) in sodium hydroxide (73 g. in 600 ml. of water) and W6 Raney nickel (20 g.) [8] were preheated to 140—150° for 3 hr., and then kept at that temperature for 3·7 hr. with a hydrogen pressure of 150 atm. Approximately 50 l. of hydrogen were absorbed (theory, 36 l.). Removal of the catalyst and acidification of the solution with hydrochloric acid precipitated 4-hydroxy*iso*phthalic acid (24 g.), m. p. 300° (decomp.), confirmed by mixed m. p. determination. Saturation of the acid filtrate with ammonium sulphate and continuous extraction with ether led to recovery of the hydrogenated products (67·2 g.). From the ethereal extracts there crystallised *4-hydroxy*cyclo*hexane*-1 : 3-*dicarboxylic acid* (16·5 g.), m. p. 188° (from ether) (Found: C, 51·1; H, 6·5%; equiv., 94·5. $C_8H_{12}O_5$ requires C, 51·1; H, 6·4%; equiv., 94·1). Infrared absorption spectrum: 3384, 3230, 2942, 2875 (sh), 2630, 2550 (sh), 1722, 1693, 1451, 1426, 1415, 1309, 1283, 1248, 1227, 1193, 1055, 1042 cm.$^{-1}$.

Fischer–Speier esterification with methanol gave the *dimethyl ester*, b. p. 170—173°/20 mm., n_D^{21} 1·4725 (Found: C, 55·1; H, 7·3. $C_{10}H_{16}O_5$ requires C, 55·5; H, 7·5%).

Esterification of the Hydrogenation Products.—The ether-soluble hydrogenation products (50·7 g.) recovered from solution, after filtration of the hydroxy*cyclo*hexanedicarboxylic acid, were esterified with ethanol and hydrochloric acid. Working up in the usual way gave acid products (9 g.), and neutral esters (54 g.) which were distilled at reduced pressure to give the following fractions: (1) b. p. <115°/1 mm.; (2) b. p. 115—118°/1 mm. (13·0 g.), n_D^{21} 1·4615; (3) b. p. 118—137°/1 mm. (12·9 g.), n_D^{21} 1·4611; residue (16·5 g.).

Examination of Fraction 2.—Hydrolysis with hot sodium hydroxide, acidification, saturation with salt, and continuous extraction with ether gave 4-hydroxy*cyclo*hexanecarboxylic acid, which recrystallised from ether–light petroleum (b. p. 60—80°) and ethyl acetate–light petroleum (b. p. 60—80°) as needles, m. p. 149—150° (Found: C, 58·6; H, 8·2. Calc. for $C_7H_{12}O_3$: C, 58·3; H, 8·4%), giving no coloration with ferric chloride solution. Infrared absorption spectrum: 3450, 2940, 2867, 2700, 2596, 1705, 1451, 1366, 1336, 1309, 1232, 1200, 1056, 1030, 982, 974, 947, 785 cm.$^{-1}$. Admixture with *trans*-4-hydroxy*cyclo*hexanecarboxylic acid [6] did not depress the m. p.; admixture with the *cis*-compound did.

Treatment of the hydroxy-acid with acetic anhydride in pyridine at room temperature furnished the *trans*-monoacetate, m. p. and mixed m. p. 135—136° (Found: C, 57·7; H, 7·6. Calc. for $C_9H_{14}O_4$: C, 58·05; H, 7·6%).

Oxidation of Ethyl trans-4-*Hydroxy*cyclo*hexanecarboxylate.—trans*-4-Hydroxy*cyclo*hexanecarboxylic acid (250 mg.) was converted into the ethyl ester by the Fischer–Speier method, and the oily product, in acetic acid (5 ml.), treated with chromium trioxide (120 mgm.) in acetic acid

[5] Campbell and Hunt, *J.*, 1950, 1379.
[6] We are greatly indebted to Drs. Campbell and Hunt for samples of the *cis*- and *trans*-4-hydroxy- and *trans*-4-acetoxy-*cyclo*hexanecarboxylic acids.
[7] Farmer and Richardson, *J.*, 1927, 59; Kon and Nandi, *J.*, 1933, 1628.
[8] Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 695.

XUM

(4 ml.) and water (1 ml.) for 48 hr. at room temperature. Recovery in the usual way gave an oil, which showed no coloration with ferric chloride solution (absence of a 2-keto-ester). The ethyl 4-oxo*cyclo*hexanecarboxylate readily furnished the 2 : 4-*dinitrophenylhydrazone*, orange needles (from ethanol), m. p. 125—126° (Found: C, 51·4; H, 5·2; N, 15·9. $C_{15}H_{18}O_6N_4$ requires C, 51·4; H, 5·1; N, 16·0%).

Examination of the Residue.—Treatment of the residue with ether gave a little unchanged 4-hydroxy*iso*phthalic acid. The recovered non-crystallisable material in ethanol (10 ml.) was refluxed with 20% sodium hydroxide solution (100 ml.). After removal of a little non-hydrolysed material with ether, acidification and continuous extraction with ether gave a viscous oil which slowly crystallised. Recrystallisation from ether–light petroleum (b. p. 40—60°) gave a *cyclo*hexene-1 : 3-dicarboxylic acid, m. p. 248—249° (Found: C, 56·5; H, 5·9%; equiv., 87. Calc. for $C_8H_{10}O_4$: C, 56·5; H, 5·9%; equiv., 85), giving a yellow coloration with ethereal tetranitromethane and none in the Liebermann–Burchard reaction. Infrared absorption spectrum: 2880, 2848, 2595, 2530, 1680, 1641, 1417, 1270, 1201, 950, 934, 745, 701 cm.$^{-1}$.

Preparation of cyclo*Hexene*-1 : 3-*dicarboxylic Acid.*—Dimethyl 4-hydroxy*cyclo*hexane-1 : 3-dicarboxylate (2 g.) was refluxed with toluene-*p*-sulphonyl chloride (2 g.) in anhydrous pyridine (15 ml.) for 2 hr., poured into dilute hydrochloric acid, and continuously extracted with ether. After benzene had been added, the solution was washed with sodium hydrogen carbonate solution and water, and dried (Na_2CO_3). Solvents were removed and the toluenesulphonate was refluxed with potassium *tert.*-butoxide in *tert.*-butyl alcohol (1·5 hr.). Water was then added and refluxing continued (1 hr.). Acidification with hydrochloric acid, and recovery with ether gave an oil which partly crystallised. Recrystallisation of these crystals from ether–light petroleum (b. p. 60—80°) gave a methyl hydrogen 4-*toluene*-p-*sulphonyl*cyclo*hexanecarboxylate*, m. p. 130—131° (Found: C, 53·9; H, 5·6; S, 9·6. $C_{16}H_{20}O_7S$ requires C, 53·9; H, 5·7; S, 9·0%).

The non-crystallisable oil was again refluxed (6 hr.) with potassium *tert.*-butoxide in *tert.*-butyl alcohol, then water added and refluxing continued (5 hr.). Working up as before and recrystallisation from ether–light petroleum (b. p. 60—80°) gave the same *cyclo*hexenedicarboxylic acid as that isolated from the residue of the hydrogenation (mixed m. p. and infrared spectrum).

We thank Mr. W. Kynaston for measurement of infrared spectra, and Monsanto Chemicals Ltd. for gifts of 4-hydroxy*iso*phthalic acid. The work described formed part of the programme of this Laboratory.

CHEMICAL RESEARCH LABORATORY,
D.S.I.R., TEDDINGTON, MIDDLESEX.

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657. *The Solubility of Anhydrous Aluminium Bromide in Pent-2-ene.*

By FRED FAIRBROTHER and JOHN F. NIXON.

THE solubility of aluminium bromide has already been measured in a number of inorganic and organic solvents,[1,2,3] including saturated and aromatic hydrocarbons and their derivatives, but not an olefin. Such measurements, however, are of special interest in view of the polymerisation of most olefins in the presence of Friedel–Crafts-type catalysts, a circumstance which renders such solubility measurements very difficult.

With many olefins examined,[4] it has not been found possible to prevent this polymerisation in the presence of aluminium bromide, even with rigorous exclusion of air and moisture. This may be a matter of degree, and possibly the small amount of moisture released when even well out-gassed Pyrex glass is sealed off, is sufficient to initiate polymerisation. However, by careful drying and pre-treatment of the solvent with aluminium

[1] Heldmann and Thurmond, *J. Amer. Chem. Soc.*, 1944, **66**, 427.
[2] Boedeker and Oblad, *ibid.*, 1947, **69**, 2036.
[3] Eley and King, *Trans. Faraday Soc.*, 1951, **47**, 1287.
[4] Fairbrother and Field, *J.*, 1956, 2614.

bromide, a stable solution of aluminium bromide in pent-2-ene can be prepared. Its ultraviolet absorption gave evidence of the existence of some solvent–solute complex formation. Its vapour pressure was consistent with a weak aluminium bromide dimer–solvent association in concentrated solution, but gave no evidence, down to −23°, of the formation of any solid complex. A solution of aluminium bromide in pent-2-ene, containing 0·017 mole of Al_2Br_6 per litre, and sealed in a quartz absorption cell, has remained without any visible change for more than two years.

Since evidence of complex formation in solution can sometimes be obtained from solubility measurements, we have now measured the solubility of aluminium bromide in pent-2-ene from about 20° to −10°. Among the recorded solubilities of aluminium bromide those most relevant are in benzene, *n*-butane, and *n*-hexane, all of which have been measured by the disappearing-crystal method. The solubility parameter δ of *n*-butane is 6·7 and that of *n*-hexane 7·30.[5] The solubility parameter of pent-2-ene can be calculated approximately from Hildebrand and Scott's equation [5] $\delta = [(\Delta H^V - RT)/V^e]^{\frac{1}{2}}$. Using the heat of vaporisation (ΔH^V) calculated by the Clausius–Clapeyron equation from the vapour-pressure data of Scott and Waddington,[6] and the molar volume V^e derived from published density data,[7] we obtain a value for δ of 7·4.

The solubilities in *n*-butane and in *n*-hexane are both well below the ideal but show fair agreement with the equation for regular solutions. Accordingly the solubility (mole fraction) is slightly greater, especially at the lower temperatures, in *n*-hexane than in *n*-butane. The highest temperature used in the present work (21·1°) is below the lowest used for the solubilities in benzene (28·2°), *n*-butane (28·3°), or *n*-hexane (30·6°), but very short extrapolation of the log x_1–$1/T$ curves enables a comparison to be made at a common temperature of 25°. One would expect, from a consideration of the respective solubility parameters of the solvents, that the solubility of aluminium bromide in pent-2-ene would be only slightly greater than that in *n*-hexane, which in turn, on a mole-fraction basis, is about 25% greater at 25° than the solubility in *n*-butane. On the other hand, the curves show that at this temperature the solubility in pent-2-ene is about 2·2 times that in *n*-hexane, 2·75 times that in *n*-butane, but only about 25% less than that in benzene, which has a solubility parameter of 9·15 and which forms a solid complex at this temperature melting incongruently at 37°. This confirms that a weak complex formation exists in solution between aluminium bromide and pent-2-ene.

Experimental.—Pent-2-ene. Commercial pent-2-ene was dried over sodium wire and fractionated. The fraction with b. p. 35·8°/749 mm. was collected and stored over bright sodium wire. Infrared absorption showed that it consisted mainly of the *cis*- and the *trans*-isomers in roughly equal amount.

Aluminium bromide. This was prepared from dry bromine and pure aluminium wire, purified by four vacuum-sublimations, and stored in fragile hook-ended ampoules.

Solubilities were measured in a closed system as described by Fairbrother, Scott, and Prophet.[8] The Table gives the solubilities (*s*) as g. of aluminium bromide dissolved by 100 g. of pent-2-ene and the Figure shows the log mole fraction of solute (x_1) as a function of $1/T$ (°K).

	Run 2						Run 3				
Temp. (°)	21·1	17·2	11·7	5·8	−3·0	−11·2	20·9	17·5	12·7	2·0	−3·7
s	77·78	69·04	60·15	53·08	42·92	37·31	75·19	66·71	64·80	43·90	38·39

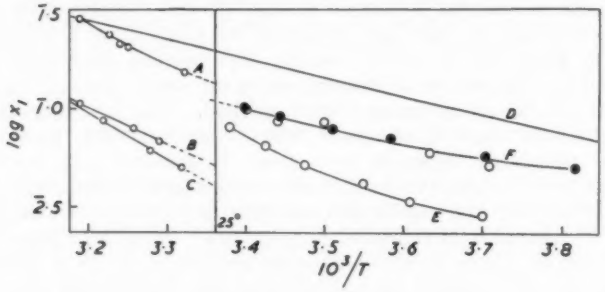
For the first run the dried pent-2-ene was pre-treated four times with pure aluminium bromide during which decreasing amounts of polymerisation occurred. When the aluminium bromide and pent-2-ene had been transferred to the solubility cell and allowed to stand, it was evident that some polymerisation had occurred, from both the colour and the separation of small amounts of a viscous liquid, which appeared to block the sintered filter. Nevertheless a series of solubility measurements were made with this solution. These are recorded as Run 1

[5] Hildebrand and Scott, "The Solubility of Non-electrolytes," Reinhold, New York, 1950.
[6] Scott and Waddington, *J. Amer. Chem. Soc.*, 1950, 4311.
[7] National Bureau of Standards, Circular 461, 1947, 46.
[8] Fairbrother, Scott, and Prophet, *J.*, 1956, 1164.

XUM

(curve *E*) on Fig. 1 and show how the presence of polymer reduces the solubility. This polymerisation could have been due to liberation of moisture from the glass during sealing off or to unremoved traces of hydrogen bromide formed during the pre-treatments; dry hydrogen bromide brings about polymerisation.

The pent-2-ene was therefore, for Run 2, further pre-treated with aluminium bromide and for Run 3 once more; in each case a greater proportion of the pent-2-ene was sacrificed in order to sweep away hydrogen bromide that might have been formed. The consistency of



the results for Runs 2 and 3 (curve *F*, black and open circles respectively) shows that the effect of pre-treatment has reached a limit.

After Run 2 a small amount of the solvent was distilled from the residual aluminium bromide: infrared absorption showed that it had the same composition as the starting material.

The Figure also gives a number of published solubilities in (*A*) benzene,[3] (*B*) *n*-hexane,[2] and (C) *n*-butane [1] and (*D*) the ideal solubility calculated by Hildebrand and Scott's equation [6] by use of data quoted by Eley and King.[3]

THE UNIVERSITY, MANCHESTER, 13. [*Received, April 24th*, 1958.]

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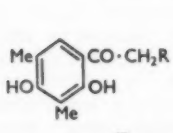
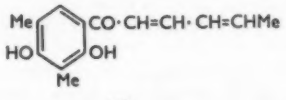
658. *A New Synthesis of Clavatol and of Sorbicillin.*

By J. F. W. McOMIE and M. S. TUTE.

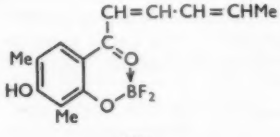
CLAVATOL, isolated from cultures of *Aspergillus clavatus*,[1] has been shown to be 2 : 4-dihydroxy-3 : 5-dimethylacetophenone (I; R = H) by Hassal and Todd,[2] who synthesised it in 68% yield by a Hoesch reaction of methyl cyanide with 2 : 4-dimethylresorcinol. Clavatol has now been synthesised in high yield by acetylation of 2 : 4-dimethylresorcinol with the commercially obtainable solution of boron trifluoride in acetic acid.



(I)



(II)



(III)

The closely related compound, sorbicillin (II), was isolated during the purification of clinical penicillin,[3] and its structure was elucidated by Cram.[4] The structure (II) was confirmed by Kuhn and Staab [5] who converted 2 : 4-dimethylresorcinol into ω-chloro-2 : 4-dihydroxy-3 : 5-dimethylacetophenone (I; R = Cl) and then carried out a

[1] Bergel, Moss, Morrison, and Rinderknecht, *J.*, 1944, 417.
[2] Hassal and Todd, *J.*, 1947, 611.
[3] Cram and Tishler, *J. Amer. Chem. Soc.*, 1948, **70**, 4238.
[4] Cram, *ibid.*, p. 4240.
[5] Kuhn and Staab, *Chem. Ber.*, 1954, **87**, 266.

Reformatsky reaction with crotonaldehyde. In this way a minute yield of sorbicillin (0·26%) was obtained, the main product being clavatol (I; R = H). Interaction of sorbic acid and 2 : 4-dimethylresorcinol in presence of boron trifluoride in ether gives a compound, $C_{14}H_{15}O_3BF_2,H_2O$, which is considered to be the monohydrate of compound (III). A similar formulation has been given to the product obtained from boron trifluoride and 2-hydroxy-3 : 5-dimethylacetophenone.[6] Attempted recrystallisation of the hydrate from aqueous methanol gave sorbicillin (II). Cram and Tishler [3,4] described this compound as an orange solid whereas Kuhn and Staab [5] stated that their product was yellow. This is clearly an example of polymorphism and we have obtained sorbicillin in both forms.

Experimental.—Commercial 2 : 4-dimethylresorcinol [7] was recrystallised from petroleum (b. p. 60—80°).

Clavatol (I; R = H). 2 : 4-Dimethylresorcinol (3·0 g.) and commercial boron trifluoride–acetic acid complex (5 ml.) were warmed on a water-bath for 3 hr. The mixture, after dilution with water (50 ml.) and addition of concentrated hydrochloric acid (3 ml.), was boiled for 1 min., then cooled and the product was collected. Recrystallisation (charcoal) from methanol gave clavatol (3·2 g., 93%) as needles, m. p. 178—180°, raised by further crystallisation to 182—184° (lit.,[3] m. p. 183°) (Found: C, 66·8; H, 6·7. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·7%). The acetate, twice recrystallised from aqueous methanol, had m. p. 96—97° (lit.,[3] m. p. 95—96°) (Found: C, 65·1; H, 6·2. Calc. for $C_{12}H_{14}O_4$: C, 65·0; H, 6·3%).

Sorbicillin (II). 2 : 4-Dimethylresorcinol (3·0 g.), sorbic acid (2·44 g.), and 45% boron trifluoride in ether (7 ml.) were warmed on a water-bath for 3 hr. After the addition of water (50 ml.) and concentrated hydrochloric acid (3 ml.), the mixture was warmed at 80° for 5 min. The solution was decanted from a viscous, red material which was well washed by decantation, then triturated with ether (100 ml.), thereby giving a bright orange solid (2·08 g.), m. p. 224—225° (Found: C, 56·4; H, 5·9; F, 12·9. $C_{14}H_{15}O_3BF_2,H_2O$ requires C, 56·4; H, 5·7; F, 12·75%). The presence of boron was shown by a green flame when a solution of the substance in ethanol–sulphuric acid was ignited. When the solid was boiled with aqueous methanol, the resulting solution deposited sorbicillin as yellow plates (1·55 g., 33%) which after one recrystallisation had m. p. 112—114° (the melt became solid and melted again at 127—143°; lit.,[3] 113—114° and 129—130°) (Found: C, 72·3; H, 7·1. Calc. for $C_{14}H_{16}O_3$: C, 72·4; H, 6·9%).

The ether filtrate (see above) was extracted with aqueous sodium carbonate which was then acidified, giving a brown solid (0·95 g., 20%). Two recrystallisations from aqueous methanol gave orange crystals of sorbicillin, m. p. 111° (with partial melting, resolidification, and remelting over a range 122—135° depending on rate of heating). A mixed m. p. with the yellow form showed no depression and, when a saturated solution of the orange form was seeded with a crystal of the yellow form, the solution deposited yellow plates. The orange and the yellow form gave the same acetate, m. p. 103—104° (lit.,[4] 103—104°) (Found: C, 70·1; H, 6·4. Calc. for $C_{16}H_{18}O_4$: C, 70·0; H, 6·5%). In ethanol the two forms gave absorption spectra which were almost identical with each other and with that recorded [3] for the orange form. Sorbicillin and its acetate gave a black colour with ferric chloride as previously noted.[4]

The authors are grateful to Dr. A. M. G. MacDonald for the fluorine analysis.

THE UNIVERSITY, BRISTOL. [*Received, April 28th*, 1958.]

[6] Kästner, "Newer Methods of Preparative Organic Chemistry," Interscience Publ. Inc., New York, 1948, p. 282.
[7] Baker, Bondy, McOmie, and Tunnicliff, *J.*, 1949, 2834.

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659. *Polyenealdehydes as Proton Acceptors.*

By Albert Wassermann.

It has been shown [1] that ω-*p*-methoxyphenylpolyenealdehydes are proton acceptors. Oxygen is more electronegative than carbon and it is probable therefore that oxygen, rather than carbon, is protonated in these reactions. In order to find out whether the oxygen atom of the methoxy- or of the aldehyde group is involved, some properties of protonated 5-phenyl-2 : 4-pentadienal were determined and they are compared, in the

		5-Phenyl-2 : 4-pentadienal *	ω-(*p*-Methoxyphenyl)-2 : 4-pentadienal
Light absorption max. (mμ)	No acid	320	350
	1·00M in $CCl_3 \cdot CO_2H$	350	380
Increment due to proton transfer (mμ)		30	30
Max. molar light absorption coeff., $10^5\varepsilon_{max.}$ (l. mole^{-1} cm.$^{-1}$)	No acid	0·38	0·35
	1·00M in $CCl_3 \cdot CO_2H$	0·35	0·30
Equil. coeff., K (l. mole^{-1}), for proton-transfer from $CCl_3 \cdot CO_2H$ to aldehyde		30 ± 4	30 ± 4
Mol. electr. conductance of protonated species, $\Lambda \times 10^7$ (l. mole^{-1} ohm^{-1} cm.$^{-1}$); soln. 1·00M in $CCl_3 \cdot CO_2H$, 1·00 × 10^{-4}M in aldehyde at 25°		2·5 ± 0·5	1·8 ± 0·3
Reversibility test with dioxan (cf. Fig. 5, ref. 1)		+	+

* Kindly placed at our disposal by Dr. M. C. Whiting; b. p. 158°/3 mm. (in nitrogen).

Table, with those of ω-*p*-methoxyphenyl-2 : 4-pentadienal.[1] In both sets of measurements the proton-donor was trichloroacetic acid and the solvent benzene, and the experimental technique was the same (temp. 20° unless otherwise stated). The figures show that the proton-acceptor properties of the two polyenealdehydes are similar, so it is concluded that the proton is taken up by the carbonyl-oxygen atom.

William Ramsay and Ralph Forster Laboratories,
University College, London, W.C.1.

[*Received, April 28th,* 1958.]

[1] Wassermann, *J.*, 1958, 1014.

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660. *Deuteration of Glyoxaline studied by Nuclear Magnetic Resonance.*

By R. J. Gillespie, A. Grimison, J. H. Ridd, and R. F. M. White.

The orientation of electrophilic substitution in glyoxaline appears to depend on the reagent;[1] nitration and sulphonation occur at the 4(or 5)-position, and diazo-coupling occurs at the 2-position. It has been suggested that this change in orientation arises because diazo-coupling involves the conjugate base of glyoxaline, while nitration and sulphonation involve the neutral molecule or the conjugate acid.[2] It was therefore of interest to determine whether the orientation of a given substitution could be changed by an alteration in the pH of the medium. Such a change is here reported for the deuteration of glyoxaline.

In D_2O alone, deuteration occurs initially in the 4 : 5-positions, and in sodium deuteroxide solution it occurs initially in the 2-position. This conclusion is supported by preliminary kinetic studies on the rate of deuteration.

Experimental.—A 4% solution of glyoxaline in D_2O was heated for 4 hr. at 250°; the D_2O was distilled off, and the glyoxaline purified by sublimation *in vacuo*. The proton nuclear magnetic resonance spectrum of a 40% solution of the product (*A*) in D_2O was then measured on a Varian Associates V-4300 high-resolution spectrometer at 40 Mc./sec., in a 5 mm. o.d.

[1] Schofield, *Quart. Reviews*, 1950, **4**, 382.
[2] R. D. Brown, Duffin, Maynard, and Ridd, *J.*, 1953, 3937.

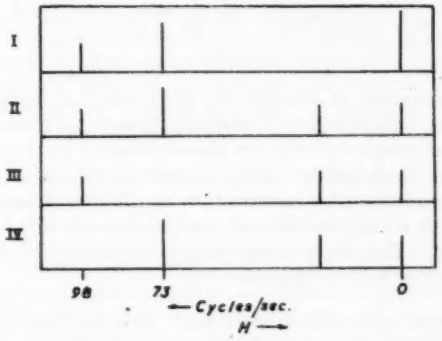
sample tube with an internal capillary of water to provide a reference signal. The spectrum obtained is shown diagrammatically (III) in the Figure.

A 5% solution of glyoxaline in D_2O containing NaOD (1·3M) was heated for 2 hr. at 150°; the product was extracted and purified as above. The nuclear magnetic resonance spectrum of a 40% solution of the product (*B*) in D_2O is also shown (IV) in the Figure.

By submitting a further sample of glyoxaline to both the above treatments, a product (*C*) was obtained, and its nuclear magnetic resonance spectrum in a 40% solution in D_2O was measured.

The nuclear magnetic resonance spectrum of a 40% solution of glyoxaline in H_2O (I) consists of two lines with an intensity ratio of 2 : 1 shifted by 73 and 98 c./sec. respectively from the

Proton nuclear magnetic resonance spectrum of glyoxaline (I, II), *4 : 5-dideuteroglyoxaline* (III), *and 2-deuteroglyoxaline* (IV).



intense line of the solvent. These lines can be identified with the two protons in the 4 : 5-positions and the single proton in the 2-position respectively. The proton on the 1-nitrogen atom exchanges rapidly with the solvent and also with the 3-position and therefore does not give rise to a separate line. This exchange also means that the protons in the 4- and the 5-position are equivalent and therefore only give rise to one line as observed. In a 40% solution in D_2O, the same spectrum is observed (II) except that the solvent line is replaced by the line due to the reference sample of water in the internal capillary tube, and a fourth line appears owing to the protons on the 1-position and the HDO molecules formed by exchange.

The spectrum of the product *A* in D_2O contains the line at 98 c./sec. due to the proton in the 2-position, the line due to the proton in the 1-position (introduced during preliminary experiments in H_2O), and the reference line, but no line at 73 c./sec. due to the protons in the 4- and the 5-position. Thus it must be 4 : 5-dideuteroglyoxaline. On the other hand, the spectrum of the product *B* contains the line at 73 c/.sec. but no line at 98 c./sec.; it must therefore be 2-deuteroglyoxaline. The product *C* gives no line at either 73 or 98 c./sec. and is therefore 2 : 4 : 5-trideuteroglyoxaline.

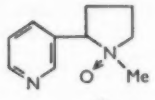
WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1.

[*Received, April 29th*, 1958.]

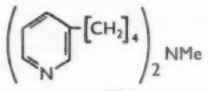
661. *New Transformation Products of Nicotine.*

By A. W. Johnson, T. J. King, and J. R. Turner.

Of the three possible *N*-oxides of nicotine only the mono-*N*-oxide (I) has been prepared previously.[1] It has now been found that oxidation of nicotine in acetic acid with hydrogen peroxide gives the di-*N*-oxide as a yellow hygroscopic oil, characterised by the formation of a monopicrate. Reduction of the di-*N*-oxide with sulphur dioxide gives the *ar*-mono-*N*-oxide (dipicrate, monopicrolonate): further reduction re-forms nicotine itself. Attempts to nitrate or mercurate nicotine *ar*-mono-*N*-oxide were uniformly unsuccessful.



(I)



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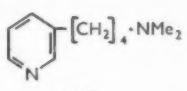

(III)

During a dehydrogenation of nicotine to nicotyrine,[2] a higher-boiling fraction was formed which has been formulated as *N*-methyl di-(4-3′-pyridylbutyl)amine (II) on the grounds of its physical properties and its decomposition by the Hofmann reaction to *NN*-dimethyl-4-3′-pyridylbutylamine (III) (characterised as its dipicrolonate). The base (III) has been synthesised by methylation of dihydrometanicotine (*N*-methyl-4-3′-pyridylbutylamine) with methyl iodide and the product identified with that obtained in the earlier experiment. The other compound, presumably 3-but-3′-enylpyridine, from the Hofmann degradation, was not isolated.

*Experimental.—Nicotine di-*N*-oxide monopicrate.* 30% Hydrogen peroxide (100 c.c.) was added to nicotine (redistilled; 40 c.c.) in glacial acetic acid (300 c.c.) and the mixture heated at 70°. After 3 hr. more hydrogen peroxide (100 c.c.) was added and the heating was continued for 8½ hr. The volume of the mixture was reduced to *ca.* 200 c.c. by distillation at the water-pump, distilled water (100 c.c.) was added, and the volume then reduced to 150 c.c. This process was repeated twice in order to remove all excess of hydrogen peroxide and peracetic acid; failure to observe this precaution may lead to a violent explosion. The volume of the mixture was finally reduced to *ca.* 100 c.c. and the clear yellow viscous residue was cooled and treated in a large beaker with excess of anhydrous sodium carbonate. The free base was extracted from the resulting paste with hot ethanol (3 × 200 c.c.) or chloroform (3 × 200 c.c.). Removal of the solvent then gave the oxide (45 g.; 92%) as a clear yellow, viscous hygroscopic oil. The *picrate*, prepared in ethanol, was triturated with acetone and crystallised from water: it decomposed above 220° (Found: C, 45·5; H, 4·0; N, 16·5. $C_{16}H_{17}O_9N_5$ requires C, 45·4; H, 4·05; N, 16·55%).

Nicotine ar-*mono*-N-*oxide.* The di-*N*-oxide of nicotine prepared in the previous experiment was dissolved in ethanol (200 c.c.) and the solution saturated with sulphur dioxide.[3] The colour of the reaction mixture quickly deepened to dark red and heat was evolved. The solution was cooled and kept overnight, after which the solvent was evaporated under reduced pressure. More alcohol (200 c.c.) was added and again removed in order to ensure complete removal of the sulphur dioxide. The resulting thick red oil was made alkaline by an excess of sodium carbonate and the mixture then extracted repeatedly with chloroform (3 × 100 c.c.). Removal of the solvent from the dried red solution gave a light red oil (32 g.). Small quantities were distilled at 90—110° (air-bath)/5 × 10^{-5} mm. The viscous, pale yellow, highly refractive, hygroscopic oil so obtained was sealed *in vacuo* before analysis (Found: C, 66·8; H, 7·7; N, 15·6. $C_{10}H_{14}ON_2$ requires C, 67·4; H, 7·9; N, 15·7%). Exposure to air caused the rapid formation of a red colour. The *dipicrate*, prepared in hot aqueous solution from the distilled product, formed fine yellow needles, m. p. 147—148° (Found: C, 41·7; H, 3·45; N, 17·8. $C_{22}H_{20}O_{15}N_8$ requires C, 41·5; H, 3·2; N, 17·6%). The *monopicrolonate* was formed from the distilled

[1] Pinner, *Ber.*, 1895, **28**, 456.
[2] Frank, Holley, and Wikholm, *J. Amer. Chem. Soc.*, 1942, **64**, 2835.
[3] Ochiai, *J. Org. Chem.*, 1953, **18**, 534.

product in acetone solution; it formed pale yellow crystals, m. p. 190—191° (Found: C, 54·5; H, 5·3; N, 18·6. $C_{20}H_{22}O_6N_8$ requires C, 54·3; H, 5·0; N, 19·0%).

For the preparation of this mono-*N*-oxide it is unnecessary to isolate the di-*N*-oxide; when the crude alcoholic solution of the di-*N*-oxide was reduced directly with sulphur dioxide yields of up to 92% of the mono-*N*-oxide (based on nicotine) before distillation were obtained.

Reduction of nicotine ar-*mono*-N-*oxide*. The oxide (redistilled; 1 g.) was heated under reflux in acetic acid (30 c.c.) in the presence of grease-free iron powder (2·2 g.) for 75 min. The solution was basified by excess of solid potassium hydroxide, and the product distilled in steam. The clear distillate gave a picrate which had m. p. 218° after crystallisation from water. The m. p. was not depressed on admixture with authentic nicotine picrate, m. p. 218°.

N-*Methyldi*-4-3′-*pyridylbutylamine* (II). Nicotine (150 g.) was dehydrogenated over palladium–asbestos at 230° rising to 280° (cf. Frank *et al.*[3]). After removal of nicotyrine (13 g.), b. p. 92—94°/0·1 mm., from the product, a second fraction (34 g.), b. p. 190—192°/0·1 mm., was obtained as a pale yellow oil. This *amine* was redistilled and the fraction (30 g.), b. p. 198—200°/0·3 mm., was collected: it had n_D^{20} 1·5411 [Found: C, 77·4; H, 8·8; N, 14·2%; *M* (Rast), 308. $C_{19}H_{27}N_3$ requires C, 76·7; H, 9·15; N, 14·15%; *M*, 297], $\lambda_{max.}$ (in 95% EtOH) 257, 263, and 269 mμ (log ε 3·77, 3·82, and 3·69 respectively). The infrared spectrum revealed no maxima between 3400 and 3200 cm.$^{-1}$, confirming the absence of >NH. The base was soluble in ethanol and acetone but insoluble in water. Potentiometric titration of a solution in 20% ethanol against 0·1N-hydrochloric acid revealed two basic groups, pK' 5·7 and 9·15 respectively.

NN-*Dimethyl*-4-3′-*pyridylbutylamine*. (i) The base (6·2 g.) from the foregoing experiment was mixed at room temperature and kept with methyl iodide (2·9 g.) in acetone (12 c.c.) for 1½ hr. The mixture was cooled and shaken at room temperature overnight with a suspension of silver oxide prepared from aqueous silver nitrate (3·8 g.) and sodium hydroxide (2·0 g.). The solid material was filtered off and the aqueous solvent removed at reduced pressure. The residual brown gum was heated (oil-bath) and decomposition which commenced at 155° became vigorous at 160°. The resulting brown oil was extracted into ether, dried, and recovered. The residue was distilled from a bulb tube and the fraction, b. p. 130—132°/16 mm. (bath-temp.), was collected as a colourless oil which darkened rapidly in air although it could be preserved *in vacuo*. The *dipicrolonate* formed yellow plates, m. p. 208—210°, from aqueous methanol (Found: C, 53·0; H, 5·0; N, 19·5. $C_{31}H_{34}O_{10}N_{10}$ requires C, 52·7; H, 4·85; N, 19·8%).

(ii) Dihydrometanicotine (5·7 g.; see below) was heated with methyl iodide (4·9 g.) in ethanol (15 c.c.) under reflux on the water-bath for 1 hr. An alcoholic solution of potassium hydroxide (2·5 g.) was added and the heating continued for a further ½ hr. After cooling, the precipitated potassium iodide was separated and most of the alcohol removed under reduced pressure. Water (20 c.c.) was added to the residue and the solvent again removed. 5N-Aqueous sodium hydroxide (20 c.c.) was added and the brown oil which formed on the surface of the solution was extracted with chloroform (2 × 100 c.c.). Removal of the solvent from the dried extract gave a brown oil which was distilled and the fraction, b. p. 93—94°/1 mm. (5·2 g.), n_D 1·5030, was collected. The dipicrolonate had m. p. 208—210° not depressed on admixture with the product from the previous experiment.

Dihydrometanicotine. Metanicotine[4] [8·2 g.; b. p. 154—156°/17 mm.; picrate, m. p. 163—165° (lit., 163°)] was hydrogenated in ethanol (60 c.c.) containing concentrated hydrochloric acid (7 c.c.) over Adams platinum catalyst. After the uptake of hydrogen had ceased, the catalyst was separated and the solvent removed. The residue was made strongly alkaline by excess of sodium hydroxide solution, and the aqueous layer saturated with sodium carbonate. The product was extracted with ether: after removal of the solvent, the residual oil was distilled under reduced pressure and the fraction, b. p. 139—144°/14 mm. (6·6 g.), was collected. The picrate had m. p. 161—163° (lit.,[4] 162—163°).

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Department of Chemistry, The University, Nottingham. [*Received, May 5th*, 1958.]

[4] Löffler and Kober, *Ber.*, 1909, **42**, 3431.

XUM

662. *The Stereoisomers of 2 : 4-Dimethyl-1 : 3-dioxolan.*

By S. A. Barker, E. J. Bourne, R. M. Pinkard, M. Stacey, and D. H. Whiffen.

Although 2 : 4-dimethyl-1 : 3-dioxolan has been known for many years,[1] it is only recently that the *cis–trans*-isomers have been separated by Lucas and Guthrie.[2] The present note advances arguments for assigning the *cis*-structure to the lower-boiling isomer (I) and the *trans*-structure to the higher-boiling isomer (II). Three lines of argument support this assignment. First, there is analogy of boiling point with the 1 : 3-dimethyl*cyclo*pentanes. Birch and Dean[3] obtained optically active forms of the higher-boiling 1 : 3-dimethyl*cyclo*pentane which must therefore be the *trans*-isomer. Secondly, and more reliably, by analogy of density with the 1 : 3-dimethyl*cyclo*pentanes: the *cyclo*pentane and the 1 : 3-dioxolan ring are of similar size and shape; at 25°, *trans*-1 : 3-dimethyl*cyclo*pentane is 0·0041 g./c.c. heavier than the *cis*-isomer, whereas the higher-boiling 2 : 4-dimethyl-1 : 3-dioxolan (II) is [2] 0·0065 g./c.c. heavier than isomer (I). Thirdly, Haresnape[4] has given reasons based on strain energies why the *cis*-isomer of 1 : 3-dimethyl*cyclo*pentane should be the more stable. Application of the same arguments to the 2 : 4-dimethyl-1 : 3-dioxolans indicate that the *cis*-isomer would again be the more stable. Equilibrium between the two isomers is readily established in acid conditions and analysis of this mixture by gas-phase chromatography showed it to contain *ca.* 65% of isomer (I) and *ca.* 35% of isomer (II), whether the starting material was pure (I) or pure (II). Hence it is concluded that isomer (I), b. p. 89·7°/742 mm., n_D^{19} 1·3950, is the *cis*-isomer, and that (II), b. p. 93·5°/748 mm., $n_D^{19.8}$ 1·3963, is the *trans*-isomer.

Experimental.—The mixture of isomers was prepared by a method similar to that of Lucas and Guthrie,[2] namely, exchange reaction between acetaldehyde di-*n*-pentyl acetal and propylene glycol. The isomers were separated by fractional distillation which was repeated until pure fractions were obtained. The fractions were analysed on a gas–liquid partition chromatography column packed with dinonyl phthalate on kieselguhr,[5] nitrogen being used as carrier. The equilibrium studies were made by passing dry hydrogen chloride into each of the pure isomers, refluxing them for 5 hr. at 100°, cooling, neutralising them with silver carbonate, and analysing the products on the chromatography column without further distillation. The quantitative analysis was by comparison with synthetic mixtures.

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Chemistry Dept., The University, Birmingham, 15.
Chemistry Dept., Royal Holloway College, Englefield Green, Surrey.

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[4] Haresnape, *Chem. and Ind.*, 1953, 1091.
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12

Recent Aspects of the Inorganic Chemistry of Nitrogen

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